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322 323 328 32Y 332
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440 453 456 45Y 470
486 500 50Y 610 611
612 620 621 624 625
62Y 630 634 635 640
650 656 660 662 670
671 672 680 682 69Y
700 720 73X 74Y 752
753 755 758 75X 761
762 764 766 76X 76Y
774 775 776 78X 78Y
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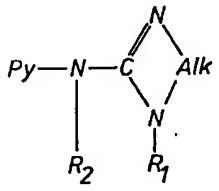
(56) Documents cited
GB 1425846
GB 1267433
(58)
(71)
(72)
(74)

# (54) Pyramidine Compounds and Pharmaceutical Preparations Containing Them

(57) Compounds of the formula I



(I)

in which Py represents an optionally substituted 4- or 5-pyrimidinyl radical bonded *via* a carbon atom to the nitrogen atom, $R_1$ and $R_2$ independently of one another represent hydrogen, lower alkyl or lower alkenyl, and Alk represents lower alkylene which separates the two nitrogen atoms by 2 to 4 carbon atoms, their tautomeric compounds and salts, exhibit hypotensive and antihypertensive effects.

## ERRATUM

SPECIFICATION No. 2 052 487 A

Front page, Heading (54), *for* Pyramidine *read* Pyrimidine

THE PATENT OFFICE
*7th June, 1982*

SEE ERRATA SLIP ATTACHED

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NB NG RA RS SM
(56) Documents cited
GB 1425846
GB 1267433
(58) Field of search
C2C
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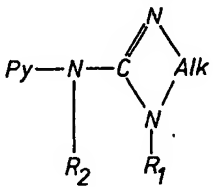
Kurt Eichenberger
(74) Agent
Thomas Sharman

(54) **Pyramidine Compounds and Pharmaceutical Preparations Containing Them**

(57) Compounds of the formula I



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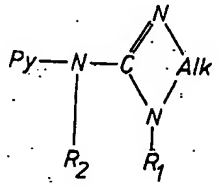
GB 2 052 487 A

ERRATA SLIP ATTACHED

SPECIFICATION

# Pyrimidine Compounds, Processes for their Preparation, Pharmaceutical preparations containing These Compounds, and Their Use in Therapeutics

The present invention relates to 2-(pyrimidinylamino)1,3-diazo-2-cycloalkene compounds, in particular of the formula



(I)

in which

Py represents an optionally substituted 4- or 5-pyrimidinyl radical bonded *via* a carbon atom to the nitrogen atom,

$R_1$ and $R_2$ independently of one another represent hydrogen, lower alkyl or lower alkenyl, and Alk represents lower alkylene which separates the two nitrogen atoms by 2 to 4 carbon atoms, their tautomeric compounds and salts, and processes for their preparation, the compounds of the formula I and their salts as pharmacologically active compounds, pharmaceutical preparations containing such compounds, and the use of the new compounds as pharmacologically active substances and for the preparation of pharmaceutical preparations.

The pyrimidinyl radical Py represents a 4- or 5-, preferably a 4-pyrimidinyl radical, which may contain, for example, lower alkyl, cycloalkyl, hydroxy, lower alkoxy, lower alkylthio, halogen, trifluoromethyl, lower alkylsulphonyl, optionally substituted phenyl or phenoxy, and/or optionally substituted amino as substituents.

In the context of the present description, radicals and compounds denoted by "lower" contain preferably up to 7, and especially up to 4, carbon atoms.

Lower alkyl represents, for example, especially methyl, and also ethyl, n-propyl, isopropyl, n-butyl, isobutyl, or tert.-butyl, and also n-pentyl, neopentyl, n-hexyl or n-heptyl.

Lower alkenyl represents, for example, especially allyl, or a 1-, 2- or 3-methylallyl group.

Lower alkoxy is, for example, especially methoxy, but may also be ethoxy, n-propoxy, isopropoxy, or n-butoxy, furthermore n-pentyloxy.

Lower alkyl sulphonyl is, for example, methylsulphonyl, ethylsulphonyl, n-propylsulphonyl or isopropylsulphonyl.

Lower alkylthio is especially methylthio, furthermore also ethylthio, isopropylthio, n-propylthio, or also a straight or branched butylthio.

A cycloalkyl radical is especially a cycloalkyl group having 3 to 6 ring carbon atoms, and is, for example, a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group.

Halogen is especially halogen of an atomic number up to 35 and represents especially chlorine, furthermore fluorine or bromine.

An optionally substituted phenyl or phenoxy radical can be substituted by one, two or three identical or different substituents. Such substituents are, for example, lower alkyl, optionally functionally modified hydroxy or mercapto, such as etherified hydroxy, for example lower alkoxy, lower alkenyloxy or lower alkylenedioxy, furthermore lower alkylthio, or halogen, trifluoromethyl, nitro, amino, including substituted amino, for example lower alkylamino or di-lower alkylamino, and optionally functionally modified carboxy, such as esterified carboxy, for example lower alkoxycarbonyl.

Lower alkenyloxy is, for example, especially vinyloxy or allyloxy.

Optionally substituted amino can be substituted by lower alkyl or optionally substituted phenyl, and is, for example, lower alkylamino or di-lower alkylamino, such as methylamino, ethylamino, dimethylamino or diethylamino, phenylamino, 4-methoxyphenylamino or 4-chlorophenylamino. It may also be substituted by lower alkylene which may contain oxygen, sulfur or optionally lower alkyl-substituted nitrogen as ring member, and may be, for example, lower alkyleneamino, for example pyrrolidino or piperidino, oxa-lower alkyleneamino, for example morpholino, thia-lower alkyleneamino, for example thiomorpholino or aza-lower alkyleneamino, for example piperazino or 4-lower alkylpiperazino, such as 4-methylpiperazino. Substituted amino may also be acylamino, such as lower alkanoylamino, for example acetylamino or propionylamino, lower alkoxycarbonylamino, for example methoxycarbonylamino or ethoxycarbonylamino, or ureido optionally substituted by lower alkyl, for example ureido, 3-methylureido or 3,3-dimethylureido.

A lower alkylene group Alk is preferably unbranched lower alkylene and especially ethylene, also 1,3-propylene, or 1,4-butylene, but may also be branched lower alkylene, such as 1,2-propylene, 2-methyl-1,2-propylene or 2,3-butylene.

Salts of compounds of the above formula I are acid addition salts, especially pharmaceutically acceptable, non-toxic acid addition salts with inorganic acids, for example hydrochloric acid,

hydrobromic acid, sulphuric acid or phosphoric acids, or with organic acids, such as corresponding carboxylic acids, for example acetic acid, propionic acid, glycolic acid, succinic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, fumaric acid, malic acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, salicyclic acid, 4-aminosalicyclic acid, 2-phenoxybenzoic acid, 2-acetoxybenzoic acid, embonic acid, nicotinic acid or isonicotinic acid, or sulphonic acids, for example methanesulphonic acid, ethanesulphonic acid, 2-hydroxyethanesulphonic acid, ethane-1,2-disulphonic acid, benzenesulphonic acid, 4-methylbenzenesulphonic acid or naphthalene-2-sulphonic acid.

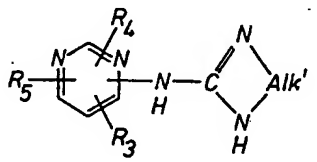
In view of the close relationship between the new compounds in their free form and in the form of their salts, including also such acid addition salts, that may be used as intermediates, for example in the purification of the new compounds or for their identification, in the preceding and following text the free compounds are to be understood optionally also as the corresponding salts in respect of general sense and intended use.

The compounds of the present invention possess valuable properties, especially pharmacological effects. Thus, they show hypotensive and antihypertensive effects which can be demonstrated in anaesthetised cats in doses from approximately 0.1 mg/kg on intravenous administration (wherein also the pressorial effects of adrenalin and nor-adrenalin are antagonised) and on renally hypertonic rats in doses from approximately 10 mg/kg/day on oral administration. Furthermore, the compounds according to the invention have an effect on the cardiac action, which can be demonstrated by means of the positively inotropic effects determined at concentrations from 100 $\mu$g/ml, and by means of the negatively chronotropic effects determined at concentrations from 10 $\mu$g/ml on the isolated guinea pig atrium. The compounds of the formula I have a favourable therapeutic index, that is to say, a favourable relationship between the effective and the toxic dose. The compounds of the present invention are therefore used as pharmacologically active compounds, especially as antihypertensives for the treatment of raised blood pressure, for example in connection with essential hypertonia, and as cardiotonic agents.

The invention relates especially to compounds of the formula I in which Py represents 4- or 5-pyrimidinyl, especially 4-pyrimidinyl, bonded *via* a carbon atom to the nitrogen atom and optionally substituted by one, two or three identical or different substituents from the group comprising lower alkyl, hydroxy, lower alkoxy, lower alkylthio, halogen, trifluoromethyl, lower alkylsulphonyl, amino; phenyl, phenoxy or phenylamino, each of which can be substituted by lower alkyl, lower alkoxy, hydroxy, amino, lower alkylamino, dilower alkylamino or halogen; lower alkylamino, di-lower alkylamino, pyrrolidino, piperidino, morpholino, thiomorpholino, lower alkanoylamino, lower alkoxycarbonylamino, ureido, 3-lower alkylureido and 3,3-di-lower alkylureido, and in which $R_1$ and $R_2$ independently of one another represent hydrogen, lower alkyl or lower alkenyl, and Alk represents lower alkylene which separates the two nitrogen atoms by 2 to 4 carbon atoms, radicals denoted by "lower" containing up to 4 carbon atoms, their tautomeric compounds and salts thereof, especially pharmaceutically acceptable, non-toxic acid addition salts.

The invention relates especially to compounds of the formula I in which Py represents 4- or 5-pyrimidinyl, especially 4-pyrimidinyl, bonded *via* a carbon atom to the nitrogen atom and optionally substituted by one, two or three identical or different substituents from the group comprising lower alkyl, lower alkoxy, phenyl, amino, lower alkylamino, di-lower alkylamino or morpholino and/or halogen, and in which $R_1$ represents hydrogen or lower alkyl and $R_2$ represents hydrogen or lower alkyl, and Alk represents lower alkylene which separates the two nitrogen atoms by 2 to 3 carbon atoms, radicals denoted by "lower" containing up to 4 carbon atoms, and halogen having an atomic weight of up to 35, and salts thereof, especially pharmaceutically acceptable, non-toxic acid addition salts.

The invention relates especially to compounds of the formula



(II),

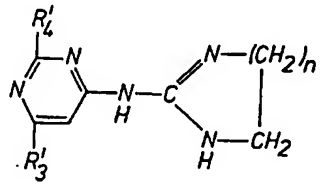
in which

Alk' represents lower alkylene having up to 4 carbon atoms which separates the two nitrogen atoms by 2 to 3 carbon atoms, especially ethylene, and each of the radicals

$R_3$, $R_4$ and $R_5$ represents hydrogen, lower alkyl having up to 4 carbon atoms, for example methyl, or lower alkoxy having up to 4 carbon atoms, for example methoxy, or halogen, for example chlorine or bromine, or di-lower alkylamino, for example dimethylamino or di-ethylamino, morpholino or phenyl, wherein preferably at least one of the radicals $R_3$, $R_4$ and $R_5$, but preferably two thereof, is different from hydrogen,

and salts thereof, especially pharmaceutically acceptable, non-toxic acid addition salts.

The invention relates especially to compounds of the formula



(III),

in which

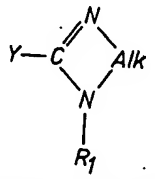
$R'_3$ and $R'_4$ independently of one another represent hydrogen, lower alkyl having up to 4 carbon atoms, for example methyl, or lower alkoxy having up to 4 carbon atoms, for example methoxy, halogen, for example chlorine, di-lower alkylamino, for example dimethylamino, wherein preferably both of the radicals $R'_3$ and $R'_4$ are different from hydrogen and are especially lower alkyl, for example methyl, lower alkoxy, for example methoxy, halogen, for example chlorine, or di-lower alkylamino, for example dimethylamino, and

n is 2 and especially 1,

and salts thereof, especially pharmaceutically acceptable, non-toxic acid addition salts.

The invention relates especially to the compounds of the formula I described in the Examples and salts thereof, especially pharmaceutically acceptable, non-toxic acid addition salts.

The compounds of the present invention can be prepared in accordance with methods known *per se*, for example by reacting a compound of the formula Py-X (IV), or a salt thereof, with a compound of the formula



(V)

or with a salt thereof, wherein one of the radicals X and Y represents an amino group of the formula —N($R_2$)—H (VI) and the other represents a group that can be split off together with hydrogen under the reaction conditions, and, if desired, converting a resulting compound of the formula I into a different compound of the formula I, and/or, if desired, converting a resulting salt into the free compound or into a different salt, and/or, if desired, converting a resulting free compound into a salt, and/or, if desired, separating a resulting mixture of isomers into the individual isomers.

A group X or Y that can be split off together with hydrogen is, for example, especially a free, or preferably an etherified, mercapto group, furthermore a reactive, functionally modified hydroxy group, or the nitroamino group. An etherified mercapto group is especially a mercapto group etherified by an optionally substituted hydrocarbon radical, especially one of aliphatic character. It is especially lower alkylthio, for example methylthio, ethylthio ot butylthio or phenyl-lower alkylthio, for example benzylthio. A reactive, functionally modified hydroxy group is a corresponding etherified or esterified hydroxy group. Such a group is, *inter alia*, lower alkoxy, for example methoxy, or halogen, for example chlorine or bromine, or lower alkylsulphonyloxy, for example methanesulphonyloxy.

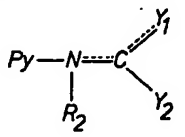
Preferably, in a compound of the formula IV the group X represents the amino group of the formula VI, whilst in a compound of the formula V the radical Y represents especially an etherified mercapto group, especially lower alkylthio, for example methylthio.

Salts of starting substances of the formula IV and V are acid addition salts, for example salts with the abovementioned acids, especially with mineral acids, such as hydrohalic acids, for example hydrochloric acid, hydriodic acid or sulphuric acid. In that case in particular the starting material that is different from an amino compound of the formula IV or V, and especially a starting material of the formula V in which Y represents an optionally etherified mercapto group or a reactive, functionally modified hydroxy group, is used in the form of an acid addition salt.

The above reaction is carried out in a manner known *per se*, for example in the absence or presence of a solvent or a mixture of solvents, if desired in the presence of an excess of the amine component used as starting material, whilst cooling or preferably whilst heating, for example at a temperature of from approximately 50°C to approximately 180°C, preferably at 160°C, if necessary in a closed vessel, optionally under pressure, and/or under an inert gas atmosphere, for example a nitrogen atmosphere.

The starting substances are known, or can be prepared in a manner known *per se*.

The new compounds can likewise be prepared by reacting a compound of the formula



(VII),

in which

$Y_1$ represents the imino group, a group that can be split off, the oxo group or thioxo group, and

$Y_2$ represents a group that can be split off, or

$Y_1$ and $Y_2$ together represent a triple-bonded nitrogen atom, when $R_2$ is hydrogen,

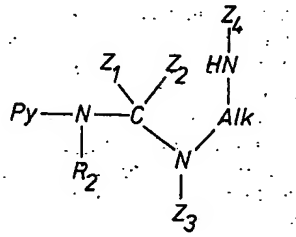
or the corresponding tautomeric form, or a salt thereof with an alkylenediamine compound of the formula $H_2N—Alk—NHR_1$ (VIII) and, if desired, carrying out additional process steps.

A group that can be split off has already been defined above under formula IV or V in connection with the substituents X or Y. A compound of the formula VII is normally used in the form of an acid addition salt, especially a salt with a mineral acid, such as a hydrohalic acid, for example hydrochloric, hydrobromic or hydriodic acid. The condensation reaction to form the ring can be effected in one or two steps.

The above reaction can be carried out in the absence or presence of a solvent, such as a, preferably, polar solvent. In that case, the process is carried out at room temperature or, preferably, at elevated temperatures, for example at approximately 50°C to approximately 200°C, wherein, in the absence of a solvent, the mixture of the two reactants (the compound of the formula VII, preferably in the form of an acid addition salt, and a compound of the formula VIII, preferably in excess) is heated to temperatures of from approximately 100°C to approximately 200°C. The reaction can be performed in a closed vessel, optionally under increased pressure, and/or under an inert gas atmosphere, such as a nitrogen atmosphere.

The starting substances are known or can be prepared in a manner known *per se*, for example those of the formula VII, for example by treating an amine compound of the formula $Py—NH—R_2$ (IVa) with a suitable isocyanate or isothiocyanate compound, such as an acyl isocyanate or acyl isothiocyanate, for example a lower alkoxycarbonyl isocyanate or lower alkoxycarbonyl isothiocyanate, such as ethoxycarbonyl isocyanate or isothiocyanate, or with an aroyl isocyanate or aroyl isothiocyanate, such as benzoyl isocyanate or benzoyl isothiocyanate (these being optionally produced *in situ*, for example by treating an alkali metal cyanate or thiocyanate or ammonium cyanate or ammonium thiocyanate with a suitable acid halide, for example an acid chloride or with a suitable acid ester), by removing the acyl group from a resulting N-acylurea compound or N-acylthiourea compound by hydrolysis, preferably in the presence of an alkaline agent, for example sodium hydroxide, and converting the corresponding urea or thiourea intermediate into the desired O- or S-substituted isourea or isothiourea compound of the formula VII by treating with a reactive ester of an alcohol, such as a lower alkylhalide, for example methylchloride, bromide or iodide, or with a di-lower alkylsulphate, for example dimethylsulphate.

In a special process variant of the preceding process, the new compounds of the formula I can likewise be obtained when a compound of the formula




(IX),

in which

$Z_1$ and $Z_2$ together represent oxygen or sulphur and

$Z_3$ represents the radical $R_1$ and

$Z_4$ represents hydrogen, or

$Z_1$ is a group that can be split off and

$Z_2$ and $Z_3$ together form a bond, and

$Z_4$ represents the radical $R_1$,

is subjected to a ring-closure reaction, and, if desired, additional process steps are carried out.

The ring closure of the above starting material of the formula IX can be carried out by means of pyrolysis, operation being carried out at temperatures of from approximately 100°C to approximately 200°C, if necessary or desired in the presence of a suitable high-boiling solvent, in a closed vessel, optionally under increased pressure, and/or under an inert gas atmosphere, for example a nitrogen atmosphere.

The starting material can be prepared in a manner known *per se*, for example by treating a compound of the formula $Py—N=C=Z$ (X) or of the formula $Py—N(R_2)—C(=X)—Hal_1$ (XI), wherein $Hal_1$ represents halogen, especially chlorine and Z represents oxygen or sulphur, with an alkylenediamine compound of the formula $H_2N—Alk—NH—R_1$ (VIII).

If desired, compounds of the formula I can be converted into different compounds of the formula I. Thus, for example, in compounds of the formula I in which $R_1$ and/or $R_2$ represents hydrogen, these

can be replaced by lower alkyl, for example, methyl or ethyl, in a manner known *per se*, for example by treating the corresponding compound with a reactive ester of a lower alkanol, such as a lower alkyl halide, for example methyl or ethyl chloride, bromide or iodide, with a dilower alkyl sulphate, for example dimethyl sulphate. In that case, operation is carried out in the absence, or preferably in the presence, of a solvent, if necessary whilst cooling or heating, for example in a temperature range from approximately 0°C to approximately 100°C, in a closed vessel, optionally under increased pressure, and/or in an inert gas atmosphere, for example a nitrogen atmosphere.

Furthermore, compounds of the formula I in which the radical "Py" is substituted by halogen, for example by chlorine or bromine, may be dehalogenated. The dehalogenation can be effected with substances having a reducing action, especially with catalytically activated hydrogen or nascent hydrogen. The exchange of the halogen is effected, for example, by hydrogen in the presence of Raney nickel in, for example, alcoholic solution, in the presence of platinum in acetic acid or, preferably, in the presence of palladium on carbon in aqueous solution when using a salt of the compound to be dehalogenated, or in a solvent that is inert for the reaction.

As solvents there may be used, for example, ethers, for example tetrahydrofuran or dioxan, lower alkanols, for example methanol or ethanol, or solvent mixtures, for example methanol/formamide. The reaction is carried out, for example, at room temperature, but may also be carried out at slightly elevated temperature, for example at a temperature of up to 60°C and under a slight excess pressure. The dehalogenation may, however, also be carried out with nascent hydrogen, for example with zinc, especially with zinc powder or, alternatively, with metallic copper. Furthermore, sodium amalgam and sodium methylate or ethylate in alcoholic solution may also be used.

Compounds of the formula I in which the radical "Py" is substituted twice by halogen, for example by chlorine or bromine, in the 2- and 6-position can be converted by reaction with an optionally substituted amine into compounds of the formula I in which a halogen atom in 2-position has been replaced by an optionally substituted amino.

The reactions with an optionally substituted amine are carried out, for example, in alcoholic solution at elevated temperature, preferably at the reflux temperature of the reaction mixture, and optionally under excess pressure.

Compounds of the formula I in which the radical "Py" is substituted twice by halogen in the 2- and 6-position can be prepared from corresponding 2-halo-6-hydroxy or 2-halo-6-lower alkoxy compounds by reacting with a halogenating agent, for example a chlorinating agent such as phosphorus oxychloride.

If lower alkoxy groups are present as substituents in the radical "Py", for example methoxy or ethoxy groups or even phenoxy groups, then these can easily be converted by acidic or basic hydrolysis into compounds of the formula I in which the radical "Py" is substituted by hydroxy. The new starting substances and processes for their preparation likewise form the subject matter of the invention.

Depending on the process conditions and the starting substances, the compounds of the formula I are obtained in free form or in the form of their salts which can be converted in the customary manner into one another or into other salts. Acid addition salts can be obtained, for example, by reacting a free compound of the formula I with an acid, especially an organic or inorganic acid, which is suitable for the formation of pharmaceutically acceptable salts. Such acids are, for example: hydrohalic acids, sulphuric acids, phosphoric acids, nitric acid, perchloric acid, aliphatic, alicyclic, aromatic or heterocyclic carboxylic or sulphonic acids, for example formic, acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, maleic, hydroxymaleic or pyruvic acid; phenylacetic, benzoic, p-aminobenzoic, anthranilic, p-hydroxybenzoic, salicylic or p-aminosalicylic acid, embonic acid, methanesulphonic, ethanesulphonic, hydroxyethanesulphonic, ethylenesulphonic acid; halobenzenesulphonic, toluenesulphonic, naphthalenesulphonic or sulphanilic acid; or ascorbic acid; methionine, tryptophan lysine or arginine. Acid addition salts of compounds of the formula I can be converted, for example, by treating with alkaline agents, such as alkali metal hydroxides, or with basic ion exchangers, into the free bases, or for example by treating with suitable ion exchangers or silver salts, into different salts.

The invention relates also to those forms of the process in which a compound obtainable at any stage of the process as an intermediate is used as starting material and the missing process steps are carried out, or the process is broken off at any stage, or in which a starting material is formed under the reaction conditions or a reaction component is optionally used in the form of a derivative, for example a salt.

Resultant mixtures of isomers can be separated into the individual isomers by methods which are known per se, e.g. by fractional distillation, crystallisation and/or chromatography.

Advantageously, for carrying out the processes according to the invention, those starting substances that lead to the initially specially mentioned groups of final products and especially to the specially described or emphasised final products are used.

The present invention additionally relates to the compounds of the formula I and their pharmaceutically acceptable, non-toxic acid addition salts for use as medicaments, especially as antihypertensives, for example for the treatment of raised blood pressure and especially to their use for

the preparation of pharmaceutical preparations, especially preparations having an antihypertensive action.

The present invention also relates to pharmaceutical preparations that contain compounds of the formula I or pharmaceutically acceptable acid addition salts of such compounds. The pharmaceutical preparations according to the invention are for enteral administration, such as oral or rectal administration, and for parenteral administration, and the preparations contain the pharmacological active substance alone or together with a pharmaceutically acceptable carrier.

The new pharmaceutical preparations contain from approximately 10% to approximately 95%, preferably from approximately 20% to approximately 90% of the active substance. Pharmaceutical preparations according to the invention in dosage unit form are, for example, dragées, tablets, capsules, suppositories or ampoules. The pharmaceutical preparations of the present invention are prepared in a manner known *per se*, for example by means of conventional mixing, granulating, dragée-making, dissolving or lyophilising processes.

Thus, pharmaceutical preparations for oral use may be obtained by combining the active substance with solid carriers and, optionally, adjuncts, optionally granulating a resulting mixture and processing the mixture or granulate, if desired or necessary after the addition of suitable adjuncts, to form tablets or dragée cores.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tri-calcium phosphate of calcium hydrogen phosphate; also binders, such as starch pastes prepared, for example, using maize, wheat, rice or potato starches, gelatin, tragacanth, methylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrolidone; and, if desired, disintegrators, such as the above-mentioned starches; furthermore, carboxymethyl starches, transversely cross-linked polyvinylpyrolidone, agar, alginic acid or a salt thereof, such as sodium alginate. Adjuncts are especially flow regulators and lubricants, for example silica, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Dragée cores are provided with suitable coatings that may be resulting to gastric juice, for which there are used, *inter alia*, concentrated sugar solutions that optionally contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions in suitable organic solvents or solvent mixtures, or, for the preparation of coatings resistant to gastric juice, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Colourants or pigments may be added to the tablets or dragee coatings, for example to identify or characterise different doses of active substance.

Other pharmaceutical preparations that may be administered orally are dry-filled capsules made of gelatin, and also soft, sealed capsules consisting of gelatin and a plasticiser, such as glycerin or sorbitol. The dry-filled capsules may contain the active substance in the form of a granulate, for example in admixture with fillers, such as lactose, binders, such as starches, and/or lubricants, such as talc or magnesium stearate, and optionally stabilisers. In soft capsules, the active substance is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, and stabilisers may likewise be added.

Pharmaceutical preparations for rectal administration are, for example, in the form of suppositories consisting of a combination of the active substance and a suppository base substance. Suitable base substances for suppositories are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols and higher alkanols. It is also possible to use gelatin rectal capsules that contain a combination of the active substance and a base substance. Suitable base substances are, for example, liquid triglycerides, polyethylene glycols and paraffin hydrocarbons.

For parenteral administration, aqueous solutions of an active substance in water-soluble form, for example in the form of a water-soluble salt, are especially suitable; also suitable are suspensions of the active substance, such as corresponding oily injection suspensions, for which suitable lipophilic solvents or vehicles, such as fatty oils, for example sesame oil, or synthetic fatty acid esters, for example ethyl oleate or triglycerides, are used; or aqueous injection suspensions that contain substances increasing viscosity, for example sodium carboxymethylcellulose, sorbitol and/or dextran and, optionally, stabilisers.

The invention likewise relates to the use of the compounds of the formula I or pharmaceutically acceptable, non-toxic salts of such compounds as pharmacologically active substances, especially as anti-hypertensive agents, preferably in the form of pharmaceutical preparations. The dosage of active substance administered is dependent on the species of warm-blooded animal, the body weight, age and individual condition, and on the form of administration. The daily dose administered to a warm-blooded animal of about 70 kg body weight is, on average, from approximately 25 to approximately 400 mg, preferably from approximately 50 to approximately 200 mg of active substance.

The following Examples illustrate the above-described invention; however, they are not intended to restrict its scope in any way whatsoever. Temperatures are given in degrees Centrigrade.

**Example 1**

7.6 g of ethylenediamine are added to a suspension of 37.4 g of the hydroiodide of N-(2,6-

dimethyl-4-pyrimidinyl)-S-methylisothiourea in 200 ml of methanol and the mixture is heated on a water bath. After 5 minutes, a clear solution is obtained, which is refluxed for one hour. The solvent is removed under reduced pressure with the aid of a rotary evaporator and the residue is heated for 2 hours at 150°C. When splitting off of methyl mercaptan has ended, the mixture is cooled, suspended in diethyl ether and then filtered. The filter residue is suspended in 50 ml of hot tert.-butanol and allowed to stand for a while. The mixture is filtered, washed with isopropanol and in this manner the hydroiodide of 2-[(2,6-dimethyl-4-pyrimidinyl)amino]-2-imidazoline is obtained, mp. 269—271°.

The salt obtainable in this manner is dissolved in 200 ml of water, the solution is rendered alkaline with 2N aqueous sodium hydroxide solution, and the crystalline material is filtered off. The free base is dissolved in chloroform, the solution is dried over magnesium sulphate and concentrated by evaporation. 2-[(2,6-dimethyl-4-pyrimidinyl)amino]-2-imidazoline in the form of white crystals is obtained as the residue, mp. 229—230°. A further quantity of the product can be obtained by extracting the aqueous mother liquor with chloroform.

The hydrochloride of 2-[2,6-dimethyl-4-pyrimidinyl)-amino]-2-imidazoline can be obtained by treating a solution of the free compound in isopropanol with the calculated amount of a 1.9N solution of hydrogen chloride in ethanol. The crystalline product melts at 298—300°.

The starting material can be prepared as follows: a suspension of 12.3 g of 4-amino-2,6-dimethylpyrimidine in 50 ml of chloroform is treated dropwise with 13.1 g of ethoxycarbonyl isothiocyanate and the mixture is refluxed for one hour. On cooling, N-(2,6-dimethyl-4-pyrimidinyl)-N'-ethoxycarbonylthiourea crystallises out and is recrystallised from 90% aqueous ethanol; it melts at 163—165°.

70 ml of a 1N aqueous sodium hydroxide solution is added to 12.7 g of N-(2,6-dimethyl-4-pyrimidinyl)-N'-ethoxycarbonylthiourea which may be obtained in this manner and the mixture is boiled for one hour. On cooling, N-(2,6-dimethyl-4-pyrimidinyl)thiourea is precipitated in the form of white crystals, mp. 236—238°.

A mixture of 20.4 g of N-(2,6-dimethyl-4-pyrimidinyl)-thiourea and 130 ml of methanol is treated with 16.7 g of methyl iodide and the mixture is refluxed for one hour, whereupon the starting material goes into solution. The solvent is evaporated under reduced pressure, and the hydroiodide of N-(2,6-dimethyl-4-pyrimidinyl)-S-methylisothiourea is obtained as the residue in the form of white crystals, mp. 200—205°; the product is processed further without purification.

**Example 2**

12.0 g of ethylenediamine in 100 ml of methanol are added dropwise to a suspension of 35.7 g of the hydroiodide of N-(2,6-dimethoxy-4-pyrimidinyl)-S-methylisothiourea in 750 ml of methanol, and the mixture is refluxed for 6 hours. After the evolution of methyl mercaptan and ammonia is complete, the reaction mixture is concentrated under reduced pressure to a volume of about 100 ml, and cooled for 16 hours. The crystalline precipitate is filtered off and washed firstly with water, and then with ethyl acetate; in this manner 2-[(2,6-dimethoxy-4-pyrimidinyl)amino]-2-imidazoline is obtained, mp. 197—200°.

39.6 ml of a 2.26N solution of hydrogen chloride in ethanol is added to a suspension of 20 g of 2-[(2,6-dimethoxy-4-pyrimidinyl)amino]-2-imidazoline and 200 ml of ethanol. The solution which may be obtained in this manner is concentrated under reduced pressure after filtration, and ethyl acetate is added thereto in portions, whereupon crystallisation commences. The crystalline material is filtered off and yields the hydrochloride of 2-[(2,6-dimethoxy-4-pyrimidinyl)amino]-2-imidazoline, mp. 193—195°.

The starting material can be obtained as follows: a mixture of 29.0 g of 4-amino-2,6-dimethoxypyrimidine and 24.5 g of ethoxycarbonyl isothiocyanate in 100 ml of chloroform is refluxed for 2 hours, then cooled, and concentrated by evaporation under reduced pressure, and the residue is suspended in 200 ml of hot 95% aqueous ethanol. The mixture is cooled, the precipitate is filtered off and washed with a mixture of ethanol and ethyl acetate. N-(2,6-dimethoxy-4-pyrimidinyl)-N'-ethoxycarbonylthiourea is obtained in the form of yellow crystals, mp. 177—180°.

A mixture of 14.3 g of N-(2,6-dimethoxy-4-pyrimidinyl)-N'-ethoxycarbonylthiourea and 90 ml of 1N aqueous sodium hydroxide solution is refluxed for 90 minutes, whereupon the starting material first of all goes into solution and the crystalline product is then precipitated. This is filtered off, washed with water and suspended in 100 ml of a hot 1:1 mixture of isopropanol and petroleum ether. N-(2,6-dimethoxy-4-pyrimidinyl)-thiourea is obtained in the form of yellow crystals, mp. 237—238°.

A suspension of 24.4 g of N-(2,4-dimethoxy-4-pyrimidinyl)thiourea in 2500 ml of acetone is treated dropwise with 64.8 g of methyl iodide and the mixture is refluxed for one hour while stirring. After a short time a clear solution is obtained, which becomes turbid shortly afterwards and deposits a crystalline material. This is filtered off, and yields the hydroiodide of N-(2,6-dimethoxy-4-pyrimidinyl)-S-methylisothiourea, mp. 185—187°, which is used without further purification.

**Example 3**

12.3 g of 4-amino-2-dimethylpyrimidine and 18.3 g of the hydroiodide of 2-methylthio-2-imidazoline are pulverised and thoroughly mixed, then heated to a bath temperature of 190°, at which

temperature splitting off of methyl mercaptan commences. The bath temperature is lowered to 170°; the mixture is left at this temperature one hour, is then cooled to 50° and the warm melt is dissolved in a 1:1 mixture of acetone and methanol. The solution is filtered and the filtrate is concentrated by evaporation to dryness under reduced pressure. The residue is taken up in a mixture of isopropanol and acetone and filtered; the residue is the hydroiodide of 2-[(2,6-dimethyl-4-pyrimidinyl)amino]-2-imidazoline and is partitioned between 2N aqueous sodium hydroxide solution and methylene chloride. The organic phase is separated, dried over magnesium sulphate and concentrated by evaporation. 2-[(2,6-Dimethyl-4-pyrimidinyl)amino]-2-imidazoline is obtained as semi-crystalline product which is taken up in water and filtered off in crystalline form, mp. 225—229°. The product displays no mixed-melting point depression with a sample of the material which may be obtained in accordance with the process of Example 1, and is identical with this according to thin-layer chromatography (system: methanol).

A further quantity of the free compound can be obtained from the isopropanol/acetone mother liquor by concentrating this by evaporation under reduced pressure dissolving the residue in water, rendering the aqueous solution alkaline with 2N aqueous sodium hydroxide solution and extracting with methylene chloride. The organic extract is concentrated by evaporation, the residue dissolved in water, and a small amount of 2N aqueous sodium hydroxide solution is added to the solution which is then cooled. The crystalline precipitate is filtered off; it melts at 227—229°.

**Example 4**

A solution of 11 g of the hydroiodide of N-(4,6-dimethoxy-2-methyl-5-pyrimidinyl)-S-methylisothiourea and 2.1 g of ethylenediamine in 100 ml of absolute ethanol is refluxed for 10 hours. The mixture is subsequently concentrated by evaporation under reduced pressure, the residue is stirred thoroughly with a saturated aqueous solution of sodium carbonate and the precipitate is filtered off. After recrystallisation from dimethylformamide, 2-[(2,4-dimethoxy-2-methyl-5-pyrimidinyl)amino]-2-imidazoline is obtained, mp. 229°.

The starting material is prepared as follows: 6 ml of benzoyl chloride is added to a solution of 4.2 g of ammonium thiocyanate in 25 ml of acetone; the mixture is boiled up for a short while, and then treated dropwise with a solution of 8.5 g of 5 amino-4,6-dimethoxy-2-methyl pyrimidine in 45 ml of acetone. Subsequently, the mixture is refluxed for 15 minutes and then the reaction solution is poured into 500 ml of water. The precipitated product is filtered off and washed well with water, then dissolved in a hot solution of 8 g of sodium hydroxide in 80 ml of water. The mixture is refluxed for 5 minutes, cooled, the pH is adjusted to 9 by the addition of 2N hydrochloric acid, whereupon N-(4,6-dimethoxy-2-methyl-5-pyrimidinyl)thiourea crystallises out, which, after recrystallisation from a mixture of water and dioxan, melts at 214—215°.

A mixture of 8.9 g of N-(4,6-dimethoxy-2-methyl-5-pyrimidinyl)thiourea and 8.5 g of methyl iodide in 800 ml of methanol is refluxed for 3 hours and then concentrated intensively under reduced pressure. The hydroiodide of N-(4,6-dimethoxy-2-methyl-5-pyrimidinyl)-S-methylisothiourea thereupon crystallises out, mp. 168—170°, and is processed further without purification.

**Example 5**

A mixture of 40.0 g of the hydroiodide of N-(2,6-dimethyl-4-pyrimidinyl)-S-methylisothiourea and 18.3 g of propylenediamine are refluxed for 6 hours. The mixture is cooled, filtered and the clear solution is evaporated to dryness under reduced pressure. The residue is taken up in 100 ml of water, and extracted three times with 150 ml of chloroform each time. The organic extract is dried over magnesium sulphate and concentrated by evaporation. In this manner, 2-[(2,6-dimethyl-4-pyrimidinyl)amino]-1,4,5,6-tetrahydropyrimidine is obtained, mp. 161—163°, which is converted into the hydrochloride as follows:

To a solution of 12 g of 2-[(2,6-dimethyl-4-pyrimidinyl)-amino]-1,4,5,6-tetrahydropyrimidine in 80 ml of isopropanol prepared at elevated temperature are added 42.7 ml of a 2.7N solution of hydrogen chloride in ethanol. The solution is concentrated under reduced pressure to approximately one third of its volume and diluted portion-wise with ethyl acetate. The crystalline precipitate is filtered off and yields the dihydrochloride of 2-[(2,6-dimethyl-4-pyrimidinyl)amino]-1,4,5,6-tetrahydropyrimidine, mp. 255—258°.

**Example 6**

A solution of 20.6 g of N-(6-chloro-2-methyl-4-pyrimidinyl)-S-methylisothiourea hydroiodide in 300 ml of methanol is added dropwise to a solution of 7.2 g of ethylenediamine in 30 ml of methanol. The internal temperature of the mixture is 65° and is maintained for 6 hours. When evolution of methyl mercaptan and ammonia is complete, the mixture is evaporated on a rotary evaporator and the residue is suspended in 150 ml of water, suction-filtered and washed with water. The crude base melts at 207—209°.

The hydrochloride is obtained by suspending 16.6 g of the crude base in 200 ml of hot ethanol and adding thereto 34.1 ml of 2.3N ethanolic hydrochloric acid, filtering the resulting clear solution with active charcoal and concentrating it on the rotary evaporator to approximately 80 ml and bringing

the hydrochloride of 2-[(6-chloro-2-methyl-4-pyrimidinyl)amino]-2-imidazoline to crystallisation with ethyl acetate and a little ether, mp. 299—301° (decomposition).

The isothiourea serving as starting material is obtained as follows:

a) 65.2 g of 4,6-dichloro-2-methylpyrimidine are stirred in 750 ml of ethanol with 100 g of liquid ammonia in an autoclave for 12 hours at 80°, the precipitated ammonium chloride is filtered off, the mixture is concentrated by evaporation on a rotary evaporator, the residue suspended hot in 1 litre of water and suction-filtered. By evaporation to approximately 100 ml further quantities of 4-amino-6-chloro-2-methylpyrimidine are obtained from the aqueous mother liquor. The combined crude products are redissolved from ethyl acetate, mp. 185—187°.

b) 28.7 g of the purified product are dissolved in 200 ml of chloroform and 50 ml of dimethylformamide; 26.2 g of ethoxycarbonyl isothiocyanate are added to the solution and the mixture is heated for 2 hours at 80°. The mixture is cooled, evaporated, and the residue, $N^1$-(6-chloro-2-methyl-4-pyrimidinyl)-$N^3$-ethoxycarbonylthiourea is recrystallised from ethanol, mp. 142—143°.

c) by hydrolysis with 1N sodium hydroxide solution (1 hour, 130°), N-(6-chloro-2-methyl-4-pyrimidinyl)thiourea of melting point 230° (discolouration and sintering) is obtained.

d) 13.5 g of this thiourea are suspended in 1500 ml of acetone, 37.8 g of methyl iodide are added and the mixture is refluxed for 2 hours. After 15 minutes dissolution occurs. The solvent is evaporated on a rotary evaporator, the crystals remaining are suspended in ether and isolated, mp. 179° (decomposition). They are the isothiourea hydroiodide mentioned as starting material.

**Example 7**

10.6 g of the 2-[(6-chloro-2-methyl-4-pyrimidinyl)-amino]-2-imidazoline base obtained according to Example 6 are dissolved in 200 ml of water and 50 ml of 1N hydrochloric acid, 1 g of 10% palladium-on-carbon is added and the mixture is shaken with hydrogen at 48° under slight excess pressure (0.2 bar). After absorption of the calculated amount (1 120 ml), the shaking is interrupted, the mixture is filtered, concentrated by evaporation on the rotary evaporator and the crystalline residue is recrystallised hot in ethanol/methanol 1:1. The resulting crystals of the dihydrochloride of 2-[(2-methyl-4-pyrimidinyl)amino]-2-imidazoline melt at 252—255°.

**Example 8**

24.0 g of N-(6-chloro-2-methoxy-4-pyrimidinyl)-S-methylisothiourea hydroiodide are dissolved in 300 ml of methanol and added dropwise to 8.0 g of ethylenediamine in 75 ml of methanol. The mixture is heated for 6 hours at reflux temperature whilst stirring, whereupon crystallisation occurs; the mixture is concentrated on the rotary evaporator and the residue is suspended in 200 ml of water. Subsequently, the residue is isolated and washed with water. In this manner, 2-(6-chloro-2-methoxy-4-pyrimidinyl)amino]-2-imidazoline of melting point 216—219° is obtained.

Hydrochloride: 11.5 g of base are suspended in 50 ml of methanol, and 1 equivalent of 2.4N ethanolic hydrochloric acid is added. The mixture is diluted with 50 ml of ethanol, filtered with Celite*, and the clear mother liquor is evaporated on the rotary evaporator to half its volume. After the addition of 100 ml of acetone, the hydrochloride of 2-[(6-chloro-2-methoxy-4-pyrimidinyl)amino]-2-imidazoline of mp. 220° precipitates as crystals.

The isothiourea used as starting material is obtained analogously to Example 6:

a) $N^1$-(6-chloro-2-methoxy-4-pyrimidinyl)-$N^3$-ethoxy-carbonylthiourea of mp. 160—164° is obtained from 63.8 g of 4-amino-6-chloro-2-methoxypyrimidine (prepared from 2,6-dichloro-4-aminopyrimidine and sodium methanolate in methanol at 80° external temperature) and 52.4 g of ethoxycarbonyl isothiocyanate in boiling acetone.

b) the hydrolysis of this ester with 150 ml of 1N sodium hydroxide solution at boiling heat yields a crystalline precipitate. Solution and precipitate are rendered weakly acidic with 10 ml of glacial acetic acid, whereupon decarboxylation occurs with foaming. N-(6-chloro-2-methoxy-4-pyrimidinyl)thiourea is isolated, mp. above 330°, and is washed with water.

c) the resulting urea is converted, as in Example 6, with methyl iodide into the isothiourea hydroiodide, mp. 167° (decomposition) mentioned as starting material.

**Example 9**

11.5 g of 2-[(6-chloro-2-methoxy-4-pyrimidinyl)amino]-2-imidazoline obtained in accordance with Example 8 are suspended in 200 ml of methanol and 100 ml of dimethylformamide (purissimum) and 2 g of 10% palladium-on-carbon catalyst are added and the mixture treated with hydrogen at 0.2 bar excess pressure and a temperature of 49°. The absorption of hydrogen progresses more slowly than in Example 7. After it has finished, the catalyst is filtered, the mother liquor is concentrated by evaporation on a rotary evaporator, 100 ml of 1N sodium hydroxide solution is added to the residue and the residue is extracted with chloroform. The chloroform residue consists of a slowly crystallising base, which is converted directly into its hydrochloride by adding to it, in 50 ml of acetone, 1 equivalent of ethanolic hydrochloric acid, then, by adding acetone and ethyl acetate, it is precipitated as crystals.

*Trade Mark

The resulting 2-[(2-methoxy-4-pyrimidinyl)amino]-2-imidazoline hydrochloride melts at 170—172° (decomposition).

**Example 10**

22.75 g of the 2-[(6-chloro-2-methoxy-4-pyrimidinyl)-amino]-imidazoline prepared in accordance with Example 8 are dissolved in 100 ml of 1N aqueous hydrochloric acid and 300 ml of water, 2 g of 10% palladium on carbon catalyst are added thereto, and the mixture is hydrogenated at 0.2 bar excess pressure and 60° internal temperature. After absorption of 2320 ml (calculated 2240 ml) the hydrogenation is broken off, the mixture is suctioned off the catalyst and concentrated fully by evaporation on a rotary evaporator. The residue is evaporated twice with 100 ml of alcohol, the crystals are suspended hot in 150 ml of isopropanol and again isolated. As a result of the methoxy group splitting off, 2-[2-(hydroxy-4-pyrimidinyl)amino]-2-imidazoline hydrochloride has formed, and has a melting point of 256—258° (decomposition).

**Example 11**

28.0 g of N-(6-chloro-2-dimethylamino-4-pyrimidinyl)-S-methylisothiourea hydroiodide are dissolved in 400 ml of methanol and added dropwise to a solution of 9.0 g of ethylene diamine in 75 ml of methanol. The mixture is stirred for 6 hours at reflux temperature, whereupon the ammonia and methyl mercaptan evolution comes to a halt and crystals are precipitated. The suspension is concentrated on a rotary evaporator to approximately 75 ml, suction-filtered, the crystalline portion is stirred with 150 ml of water, is isolated, and washed with water and isopropanol. The resulting 2-[(6-chloro-2-dimethylamino-4-pyrimidinyl-amino]-2-imidazoline melts at 268—271°. After recrystallisation from dimethylsulfoxide-methanol the product melts at 278—279°.

The resulting base has the calculated amounts of 2N aqueous hydrochloric acid added to it, whereupon the hydrochloride partially crystallises. By addition of 4 times the amount of water, at 75° a clear solution is obtained which, after filtration, is evaporated on a rotary evaporator, the residue is suspended in isopropanol, suction-filtered and washed with ethyl acetate. The hydrochloride melts at 279—280°.

At room temperature 3.42 g of methanesulphonic acid are added to a suspension of 7.8 g of base in 300 ml of water, whereupon a clear solution is obtained. The solution is evaporated to dryness, and the residue is recrystallised from methanol/ether. The methanesulphonate obtained in this manner melts at 256—259°.

The isothiourea used as starting material is obtained analogously to Example 6:

a) 4-Amino-6-chloro-2-dimethylaminopyrimidine of melting point 151—152° is prepared from 4-amino-2,6-dichloropyrimidine with dimethylamine in methanol in exothermic reaction. 34.5 g of this compound are reacted with 26.2 g of ethoxycarbonyl isothiocyanate in 150 ml of acetone under reflux to give $N^1$-(6-chloro-2-dimethylamino-4-pyrimidinyl)-$N^3$-ethoxy-carbonylthiourea, mp. 206—208°.

b) The hydrolysis of this compound with 170 ml of 1N sodium hydroxide solution at reflux temperature yields a thick crystalline mash which is suction-filtered and washed throughly with water. The resulting N-(6-chloro-2-dimethylamino-4-pyrimidinyl)thiourea melts at 235° (decomposition).

c) 29.0 g of this thiourea are suspended in 2.9 litres of acetone and 71 g of methyl iodide are added. On refluxing, the suspension goes into solution and crystallises out again shortly afterwards. The mixture is cooled and the crystalline precipitate of N-(6-chloro-2-dimethylamino-4-pyrimidinyl)-S-methylisothiourea hydroiodide of melting point 220° (decomposition) is isolated.

**Example 12**

11.1 g of 2-[(6-chloro-2-dimethylamino-4-pyrimidinyl)-amino]-2-imidazoline base (prepared according to Example 11), are dissolved with 19.5 ml of 1N hydrochloric acid and 80 ml of water, and hydrogenated with hydrogen with 2 g of 10% palladium-on-carbon at 0.2 bar excess pressure. The temperature is 52—55°. After 15 hours, the calculated amount of hydrogen (438 ml) has been taken up. The solution is filtered off the catalyst, the aqueous mother liquor is concentrated on a rotary evaporator, the residue is dissolved in 75 ml of isopropanol and is allowed to crystallise. The resulting 2-[(2-dimethylamino-4-pyrimidinyl)-amino]-2-imidazoline dihydrochloride melts at 275—278° (decomposition).

**Example 13**

In the same manner as described in Example 11, from 11.5 g of ethylenediamine in 100 ml of methanol, to which 38.0 g of N-(6-chloro-2-diethylamino-4-pyrimidinyl)-S-methylisothiourea hydroiodide in 200 ml of methanol are added dropwise, there is obtained after 6 hours' stirring under reflux 2-[(6-chloro-2-diethylamino-4-pyrimidinyl)-amino)-2-imidazoline base of melting point 231—232°. By suspending 21.5 g of the base in 50 ml of methanol and adding two equivalents (67 ml) of 2.39N ethanolic hydrochloric acid, followed by 300 ml of ethyl acetate, the dihydrochloride is obtained, which, on drying in high vacuum, is transformed into the monohydrochloride of melting point 203—205°.

The starting material for the above-described synthesis can be obtained in analogy to Example 11:

a) from 4-amino-2,6-dichloropyrimidine with an excess of diethylamine in methanol at 80° external temperature, 4-amino-6-chloro-2-diethylaminopyrimidine melting at 110° is obtained which is used further as crude product;

b) by reacting 43.6 g of this pyrimidine with 28.5 g of ethoxycarbonyl isothiocyanate in boiling acetone, $N^1$-(6-chloro-2-diethylamino-4-pyrimidinyl)-$N^3$-ethoxycarbonyl thiourea melting at 141—145° is obtained;

c) by hydrolysis of 48.0 g of the resulting ester with 250 ml of 1N sodium hydroxide solution under reflux, N-(6-chloro-2-diethylamino-4-pyrimidinyl)thiourea of melting point 175—180° is obtained; and

d) from this crude thiourea (35.8 g) with 40 g of methyl iodide in 750 ml of acetone under reflux, N-(6-chloro-2-diethylamino-4-pyrimidinyl)-S-methylisothiourea hydroiodide of melting point 178—180° (decomposition) used as starting material is obtained.

**Example 14**

In the same manner as described in Examples 11 and 13, 2-[(6-chloro-2-di-n-butylamino-4-pyrimidinyl)amino]-2-imidazoline and its hydrochloride are obtained from N-(6-chloro-2-di-n-butylamino-4-pyrimidinyl)-S-methylisothiourea hydroiodide and ethylenediamine in methanol. The free base melts at 167—168°, and the hydrochloride at 148—150°.

The starting material for this dibutylamino derivative is obtained in the same reaction sequence as described in Examples 11 and 13 from 4-amino-2-di-n-butylamino-6-chloro-pyrimidine.

**Example 15**

10.3 g of ethylenediamine are introduced into 40 ml of methanol and, whilst stirring, at 70° 30.3 g of N-(6-dimethylamino-2-methyl-4-pyrimidinyl)-S-methylisothiourea hydroiodide in 350 ml of methanol are added dropwise and the reaction mixture is maintained for 6 hours at this temperature. The solvent with the suspended crystals is brought to dryness on a rotary evaporator and the residue is suspended in 300 ml of water. A sample shows that the crystals still contain small amounts of hydroiodide. They are therefore dissolved in 200 ml of 2N hydrochloric acid and precipitated with 5N sodium hydroxide solution. The crystalline base is isolated, washed twice with warm water, then treated with isopropanol and ether. In this manner, 2-[(6-dimethylamino-2-methyl-4-pyrimidinyl)amino]-2-imidazoline mp. 286—288° is obtained which is shown to be analytically pure.

Its hydrochloride is obtained as monohydrochloride, mp. 281—283°, by suspending the base in isopropanol, adding 1 equivalent of ethanolic 2.3N hydrochloric acid, and precipitating with ethyl acetate.

The starting material for the above described synthesis can be obtained analogously to Examples 11 and 13:

a) from 4-amino-6-chloro-2-methyl pyrimidine melting at 185—187° used in Example 6 and 4 times the theoretical amount of dimethylamine in methanol, at 120° in a pressurized vessel 4-amino-6-dimethylamino-2-methyl pyrimidine of mp 176—179° is obtained;

b) by reacting 29.0 g of this pyrimidine with 25.0 g of ethoxycarbonyl isothiocyanate in boiling chloroform, $N^1$-(6-dimethylamino-2-methyl-4-pyrimidinyl)-$N^3$-ethoxy-carbonylthiourea is obtained, melting at 140—143° (after recrystallisation from alcohol);

c) by hydrolysing 31.0 g of the resulting ester with 200 ml of 1N sodium hydroxide solution at boiling temperature, N-(6-dimethylamino-2-methyl-4-pyrimidinyl)thiourea melting at 245—247° is obtained; and

d) from 19.3 g of this resulting thiourea, with 51.9 g of methyl iodide in 2000 ml of acetone and 200 ml of methanol N-(6-dimethylamino-2-methyl-4-pyrimidinyl)- S-methyl-isothiourea hydroiodide melting at 225—227° is obtained under reflux.

**Example 16**

To a boiling solution of 9.5 g of ethylenediamine in 50 ml of methanol are added dropwise 26.0 g of N-(2,6-dihydroxy-5-pyrimidinyl)-S-methylisothiourea hydroiodide in 500 ml of warm methanol, and the whole is refluxed for 15 hours. After a short time, a white precipitate begins to form. The mixture is cooled, filtered with suction and the precipitate, which, in addition to the imidazoline base also contains hydroiodide that is not readily soluble and non-reacted isothiourea hydroiodide, is washed several times in the course of 12 hours with water of 50° which contains 10% methanol. The melting point thereby rises from 268° (decomposition) to 290° (decomposition) and finally remains constant at 328—330°. The latter melting point corresponds to the pure 2-[(2,6-dihydroxy-5-pyrimidinyl)amino]-2-imidazoline which is present for the most part in its tautomeric form, 2-[(2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinyl)amino]-2-imidazoline.

The hydrochloride is obtained by dissolving 7.5 g of the base in 38.5 ml of 1N hydrochloric acid under heat. The solution is filtered, concentrated by evaporation on a rotary evaporator, the residue is evaporated with 100 ml of ethanol, 50 ml of ethyl acetate and 50 ml of isopropanol are added to the

residue and the whole is stirred until crystallisation occurs. Mp. 275° (decomposition). Hydrochlorides (mp. 130°, decomposition) containing water of crystallisation are dried in high vacuum until a melting point of 275° is reached.

The starting material for the above described synthesis is obtained in analogy to Examples 11, 13 and 15 in the following manner:

a) 12.5 g of 5-aminouracil are suspended in 150 ml of dimethyl sulphoxide and 13.1 g of ethoxycarbonyl isothiocyanate are added. The mixture is stirred for 3 hours at 60°, a clear solution is obtained, this is poured into water, suction-filtered and $N^1$-(2,6-dihydroxy-5-pyrimidinyl)-$N^3$-ethoxycarbonylthiourea is obtained which is suspended in boiling acetone to purify it. Mp. >300°;

b) by hydrolysing this compound (12.9 g) for one hour with 150 ml of 1N sodium hydroxide solution, at reflux temperature, by cooling, adding a total of 50 ml of glacial acetic acid, crystalline N-(2,6-dihydroxy-5-pyrimidinyl)-thiourea of mp. >300° is obtained, which is suspended in hot isopropanol to purify it;

c) by reacting 27.9 g of this compound with 21.3 g of methyl iodide in 1800 ml of methanol and 1000 ml of dimethylformamide at 80°, N-(2,6-dihydroxy-5-pyrimidinyl)-S-methylisothiourea hydroiodide of melting point 245° (decomposition) is obtained.

**Example 17**

To a solution of 8.5 g of ethylenediamine in 80 ml of methanol, the solution of 26.0 g of N-(2,6-diethyl-5-methyl-4-pyrimidinyl)-S-methylisothiourea hydroiodide in 250 ml of methanol is added dropwise. The mixture is stirred and refluxed for 12 hours, evaporated in a rotary evaporator to dryness, dissolved in methylene chloride, washed twice with water, the solvent is again evaporated, the crystalline residue is suspended in ethanol and white crystals of the base melting at 128—131° are obtained, which are converted into the hydrochloride of 2-[(2,6-diethyl-5-methyl-4-pyrimidinyl)amino]-2-imidazoline by dissolving 13.8 g of the base in ethanol, adding 32.0 ml of 1.82N ethanolic hydrochloric acid and bringing the hydrochloride to crystallisation with a little ether. Mp. 190—192°.

The starting material for the above described synthesis can be obtained analogously to Examples 11, 13, 15 and 16 as follows:

a) From 33.0 g of 4-amino-2,6-diethyl-5-methylpyrimidine ("kyanethin") in 200 ml of acetone and 50 ml of dimethylformamide, and 26.2 g of ethoxycarbonyl isothiocyanate, after 3 hours refluxing $N^1$-(2,6-diethyl-5-methyl-4-pyrimidinyl)-$N^3$-ethoxycarbonylthiourea of melting point 86—89° is obtained.

b) From 49.5 g of this compound, N-(2,6-diethyl-5-methyl-4-pyrimidinyl)thiourea melting at 151—154° is obtained by hydrolysing with 100 ml of 2N sodium hydroxide solution, under reflux, and neutralising with glacial acetic acid to pH 5.

c) From 17.1 g of this compound and 43.2 g of methyl iodide in 400 ml of hot acetone, N-(2,6-diethyl-5-methyl-4-pyrimidinyl)-S-methylisothiourea hydroiodide melting at 180—182° is obtained.

**Example 18**

27.0 g of N-(2-phenyl-4-pyrimidinyl)-S-methylisothiourea hydroiodide in 300 ml of methanol, are added dropwise to 9.0 g of ethylenediamine in 100 ml of methanol. The mixture is heated at 80° for 6 hours, whilst stirring, evaporated to dryness on a rotary evaporator, the crystalline compound is suspended in water, then in isopropanol-ether mixture and in this manner 2-[(2-phenyl-4-pyrimidinyl)-amino]-2-imidazoline melting at 230—232° is isolated.

From 15 g of the imidazoline base, the dihydrochloride is obtained as crystals melting at 255—257° by suspending in methanol (50 ml), adding 2 equivalents of 2.3N ethanolic hydrochloric acid (54.4 ml), filtering the resulting solution and adding ethyl acetate.

The above used starting material is obtained *via* the following stages:

a) from 51.3 g of 4-amino-2-phenyl pyrimidine and 40 g of ethoxycarbonyl isothiocyanate in 400 ml of boiling acetone, $N^1$-(2-phenyl-4-pyrimidinyl)-$N^3$-ethoxycarbonyl-thiourea melting at 185—188° is obtained;

b) from 66.4 g of the ester, N-(2-phenyl-4-pyrimidinyl)-thiourea melting at 237° (decomposition) is obtained by hydrolysis with 300 ml of 1N sodium hydroxide solution at boiling heat;

c) from 38.3 g of this thiourea and 100 g of methyl iodide in 3.8 litres of boiling acetone, N-(2-phenyl-4-pyrimidinyl)-S-methylisothiourea hydroiodide melting at 200° (decomposition) is obtained.

**Example 19**

22.8 g of N-(2-phenyl-4-pyrimidinyl)-S-methylisothiourea hydroiodide (starting material from Example 18) and 9.4 g of propylenediamine (1,3-diaminopropane) are refluxed in 300 ml of methanol for 6 hours whilst stirring. The mixture is evaporated to dryness on the rotary evaporator, the oily residue is partitioned between 300 ml of water and 300 ml of chloroform, and the organic phase is dried and evaporated and brought to crystallisation with 50 ml of ethyl acetate and 25 ml of ether. The resulting 2-[(2-phenyl-4-pyrimidinyl)amino]-1,4,5,6-tetrahydropyrimidine melts at 166—169°.

From this base, the monohydrochloride of melting point 255° (sintering from 246°) is obtained in acetone with one equivalent of ethanolic hydrochloric acid.

**Example 20**

A solution of 44.1 g of the hydroiodide of N-(2-methyl-5-pyrimidinyl)-S-methylisothiourea and 17.6 g of ethylenediamine in 400 ml of absolute ethanol is refluxed for 12 hours. After filtration and concentration by evaporation to dryness, the oily residue is partitioned between 400 ml of chloroform and approximately 325 ml of a semi-saturated soda solution, the layers are separated and subsequently the aqueous layer is extracted several times with chloroform. The combined chloroform extracts, after drying and concentration, when petroleum ether is added to them give a crystalline precipitate of 2-[(2-methyl-5-pyrimidinyl)-amino]-2-imidazoline melting at 187—189°.

Ether and a little ethyl acetate are slowly added to a solution produced by heating 21.3 g of the above base in 200 ml of isopropanol and 12.2 g of methanesulphonic acid, whereupon crystallisation gradually occurs. The resulting methanesulphonate of 2-[(2-methyl-5-pyrimidinyl)-amino]-2-imidazoline, after recrystallisation from a mixture of methanol and acetone, melts at 149—151°.

The hydroiodide of N-(2-methyl-5-pyrimidinyl)-S-methylisothiourea can be prepared as follows:

Approximately 42 g of ethoxycarbonyl isothiocyanate are added dropwise to a solution of 26.5 g of 2-methyl-5-aminopyrimidine in 750 ml of chloroform at room temperature and the mixture is then stirred for one hour at room temperature and for two and a half hours under reflux. After concentration by evaporation to dryness, the solid residue is recrystallised from boiling absolute ethanol. In this manner, N-(2-methyl-5-pyrimidinyl)-N'-ethoxycarbonylthio-urea melting at 183—185° is obtained.

390 ml of a 1N aqueous sodium hydroxide solution are added to 53 g of the N-(2-methyl-5-pyrimidinyl)-N'-ethoxy-carbonyl thiourea thus obtained. The resulting solution is refluxed for 3 hours, cooled, and the pH is adjusted to approximately 8 by the addition of 6N hydrochloric acid, whereupon N-(2-methyl-5-pyrimidinyl)thiourea crystallises out, and, after recrystallisation from boiling absolute ethanol, melts at 191—193° with decomposition.

A suspension of 28.75 g of the above N-(2-methyl-5-pyrimidinyl)thiourea and 113 g of methyl iodide in 1400 ml of acetone is heated to reflux, whereupon the starting material dissolves. Approximately 20 minutes later, crystals precipitate. The solution is boiled for a further one and three-quarter hours, is cooled to room temperature, the hydroiodide of N-(2-methyl-5-pyrimidinyl)-S-methylisothiourea is suction-filtered and washed with a little acetone and ether. Melting point approximately 152° with decomposition.

By concentration *in vacuo*, a further quantity of the crystalline hydroiodide can be obtained from the mother liquor.

**Example 21**

In an analogous manner the following are obtained:

a) 2-[(5-pyrimidinyl)amino]-2-imidazoline melting at 232—234° from $N^1$-(5-pyrimidinyl)-$N^3$-ethoxycarbonylthiourea, mp. 191—193°; the hydrochloride melts at 241—243° (decomposition);

b) 2-[(2-n-butyl-5-pyrimidinyl)amino]-2-imidazoline of melting point 145—147° from $N^1$-(2-n-butyl-5-pyrimidinyl)-$N^3$-ethoxycarbonylthiourea, mp. 134—135°; the methanesulphate melts at 100 to 102°;

c) 2-[(2-phenyl-5-pyrimidinyl)amino]-2-imidazoline of melting point 250—252° from $N^1$-(2-phenyl-5-pyrimidinyl)-$N^3$-ethoxycarbonylthiourea, mp. 195—198°; the hydrochloride melts at 230—233°.

d) 2-[(6-chloro-2-(4-morpholino)-4-pyrimidinyl)amino]-2-imidazoline of melting point 250—252° from $N^1$-(6-chloro-2-(4-morpholino)-4-pyrimidinyl)-$N^3$-ethoxy-carbonylthiourea, mp. 185—189°; the hydrochloride melts at 274—275°.

**Example 22**

6.12 g of ethylenediamine are added to a suspension of 18 g of N-(2-dimethylamino-6-methyl-4-pyrimidinyl)-S-methylisothiourea hydroiodide in 180 ml of ethanol, whereupon a clear solution is formed. Subsequently, the mixture is refluxed for 6 hours. The reaction product that has already precipitated during the reaction is suction-filtered and washed with isopropanol and ether. The resulting 2-[(2-dimethylamino-6-methyl-4-pyrimidinyl)amino]-2-imidazoline melts at 280—283°.

4.6 g of methanesulphonic acid are added to a suspension of 10.35 g of this base in 300 ml of absolute ethanol and the mixture is heated on a water bath, whereupon a clear solution forms. The mixture is evaporated to half its volume, and 175 ml of ether are added gradually, whereupon the methanesulphonate of melting point 226—228° is deposited.

The isothiourea used as starting material is obtained analogously to Example 6:

4-amino-2-dimethylamino-6-methylpyrimidine is reacted with 11.15 g of ethoxycarbonyl isothiocyanate in 200 ml of absolute tetrahydrofuran under reflux to give $N_2$-(2-dimethylamino-6-methyl-4-pyrimidinyl)-$N^3$-ethoxycarbonylthiourea of melting point 199—201°.

This compound is refluxed with 180 ml of sodium hydroxide solution and 100 ml of ethanol for 2 hours. The mixture is concentrated *in vacuo* and adjusted to pH 7.5 with 2N hydrochloric acid; the crystalline mash is suction-filtered. After recrystallisation from boiling alcohol, the resulting N-(2-dimethylamino-6-methyl-4-pyrimidinyl)-thiourea melts at 241—243°.

10.9 g of this thiourea are suspended in 1.2 litres of acetone and 29.5 g of methyl iodide are

added thereto. On refluxing, the suspension goes into solution and crystallises out again shortly afterwards. The mixture is refluxed for a further hour and the crystalline precipitate of N-(2-dimethylamino-6-methyl-4-pyrimidinyl)-S-methylisothiourea hydroiodide melting at 211—214° is suction-filtered.

**Example 23**

In one portion, 6.4 g of N-(2-diethylamino-5-pyrimidinyl)-S-methylisothiourea hydroiodide are added to a solution of 2.1 g of ethylenediamine in 40 ml of methanol, and the mixture is refluxed for 6 hours. The yellow reaction solution is concentrated by evaporation under reduced pressure. 75 ml of 2N sodium hydroxide solution are added to the residue and the mixture is extracted by shaking with petroleum ether to remove the 5-amino-2-dimethylaminopyrimidine. The aqueous-oily layer is extracted several times with ethyl acetate. After recrystallisation from ethyl acetate, 2-[(2-diethylamino-5-pyrimidinyl)amino]-2-imidazoline of melting point 169—171° is obtained from the evaporated ethyl acetate extracts.

0.94 g of methanesulphonic acid is added to 1.1 g of the resulting base dissolved in 35 ml of isopropanol. On addition of ether, the dimethanesulphonate of melting point 144—147° crystallises out.

The isothiourea used as starting material is prepared as follows:

29.2 g of N,N-diethyl guanidine hemisulphate and 28.5 g of malonic acid diethyl ester are added to a solution of 12.4 g of sodium in 360 ml of ethanol, and the mixture is refluxed for 3 hours. Subsequently, the reaction mixture is concentrated by evaporation. The residue is dissolved in 400 ml of water and adjusted to pH 3.5 with concentrated hydrochloric acid, whereupon 2-diethylamino-4,6-dihydroxypyrimidine of melting point 235—240° (decomposition) is precipitated.

At an internal temperature of 15—18°, within 25 minutes 65 ml of glacial acetic acid are added dropwise to 25 ml of fuming nitric acid (d=1.52). Whilst stirring well, within 15 minutes 21 g of 2-diethylamino-4,6-dihydroxypyrimidine are then added in portions. When the addition has ended, the mixture is stirred for a further 2 hours at room temperature. The reaction mixture is poured onto ice and the precipitated 2-diethylamino-4,6-dihydroxy-5-nitropyrimidine melting at 280—282° (decomposition) is suction-filtered.

25.1 g of 2-diethylamino-4,6-dihydroxy-5-nitropyrimidine are refluxed for 90 minutes in 150 ml of phosphorus oxychloride and 38 ml of diethylaniline. The black reaction solution is intensively concentrated under reduced pressure. The oily residue is poured onto ice and extracted with ether. The residue obtained from the ether phases is recrystallised from cyclohexane. In this manner, 2-diethylamino-4,6-dichloro-5-nitropyrimidine of melting point 91—93° is obtained.

24.5 g of 2-diethylamino-4,6-dichloro-5-nitro-pyrimidine are hydrogenated in 250 ml of ethanol with 12 g of Raney nickel as the catalyst. After absorption of 3 mole equivalents of hydrogen, the mixture is filtered off the catalyst and the filtrate acidified with 8N alcoholic hydrochloric acid. Subsequently, the solution is intensively concentrated under reduced pressure until crystallisation commences. The crystals are suction-filtered and in this manner 2-diethylamino-4,6-dichloro-5-aminopyrimidine dihydrochloride is obtained.

20.5 g of 2-diethylamino-4,6-dichloro-5-aminopyrimidine dihydrochloride are hydrogentated at room temperature in 600 ml of ethanol with 2 g of palladium-on-carbon (5%) as the catalyst, and 23 g of anhydrous sodium acetate. After absorption of 2 mole equivalents of hydrogen, the mixture is filtered to remove the catalyst and the precipitated inorganic salts, and the filtrate is rendered strongly acidic with excess 8N alcoholic hydrochloric acid and concentrated by evaporation to dryness under reduced pressure. The oily residue, which contains 2-diethylamino-5-aminopyrimidine dihydrochloride, is refluxed in 250 ml of chloroform with 55 g of ethoxycarbonyl isothiocyanate and 25 ml triethylamine for 3 hours. The reaction solution is concentrated by evaporation to dryness *in vacuo*. The residue is chromatographed on silica gel by eluting with toluene with an increasing addition of ethyl acetate. In this manner $N^1$-(2-diethylamino-5-pyrimidinyl)-$N^3$-ethoxycarbonylthiourea of melting point 130—132° is obtained.

7.35 g of $N^1$-(2-diethylamino-5-pyrimidinyl)-$N^3$-ethoxycarbonylthiourea are refluxed for 1 hour with 70 ml of 1N sodium hydroxide solution. After cooling, the reaction mixture is adjusted to pH 8, the precipitated crystals are suction-filtered, and recrystallised from ethyl acetate-petroleum ether. In this manner N-(2-diethylamino-5-pyrimidinyl)thiourea melting at 162—166° is obtained.

4.05 g of the above thiourea are stirred for 2 hours under reflux in 25 ml of acetone with 8.1 ml of methyl iodide. The reaction solution is concentrated by evaporation and the residue crystallised from ethyl acetate with the addition of ether. In this manner N-(2-diethyl-amino-5-pyrimidinyl)-S-methylisothiourea hydroiodide of melting point 175—177° is obtained.

**Example 24**

A mixture of 6.6 g of 2-[(6-chloro-2-dimethylamino-5-methyl-4-pyrimidinyl)amino]-2-imidazoline hydrochloride, 200 ml of acetic acid and 30.25 ml of 1.5N hydrochloric acid in glacial acetic acid is hydrogenated at 35°C and a pressure of 4 bars with the addition of 1.3 g of a 10% palladium-on-carbon catalyst until absorption of 1 mole equivalent of hydrogen. Thereafter the mixture is filtered to

remove the catalyst, and the filtrate concentrated by evaporation under reduced pressure. After recrystallisation of the residue from ethyl alcohol, with the addition of active carbon 2-[2-dimethylamino-5-methyl-4-pyrimidinyl)amino]-2-imidazoline hydrochloride which melts at 263° (decomposition) is obtained as a colourless crystallisate.

The starting material is prepared in accordance with Example 29.

**Example 25**

5.26 g of N-(6-chloro-2-dimethylamino-4-pyrimidinyl)-dithiocarbamic acid methyl ester are refluxed for 8 hours with 1.3 g of ethylenediamine in 50 ml of acetonitrile. The solvent is then evaporated *in vacuo* and 1-(6-chloro-2-dimethylamino-4-pyrimidinyl)-3-(2-aminoethyl)thiourea obtained as residue is freed from moisture still adhering to it by evaporation with toluene.

The dark oil remaining is heated in 50 ml of diphenyl ether for 2 hours at 200°. Thereupon the solvent is distilled off in a bulb tube under vacuum, the semicrystalline residue is stirred with water, filtered, and the product is washed with water and isopropanol. The resulting 2-[(6-chloro-2-dimethylamino-4-pyrimidinyl)amino]-2-imidazoline melts at 278—279°.

N-(6-chloro-2-dimethylamino-4-pyrimidinyl)dithiocarbamic acid methyl ester used as starting material can be prepared in the following manner:

8 g of 4-amino-5-chloro-2-dimethylaminopyrimidine are introduced into 100 ml of dimethylformamide. To this mixture are added in portions over 5 minutes 2.4 g of sodium hydroxide at 0°, and the mixture is stirred for 15 minutes. 1.5 ml of carbon disulphide are added dropwise at 0—5°, and the whole is stirred for 30 minutes. 1.2 g of sodium hydride are added, again at 0—5°, the mixture is stirred for 15 minutes, and then at the same temperature 0.75 ml of carbon disulphide is added and stirring is continued for a further 30 minutes. After repeated addition of 1.2 g of sodium hydride and 0.75 ml of carbon disulphide in the above-described manner, after 30 minutes at 0—5° 2.8 ml of methyl iodide are added and the reaction solution is allowed to heat up to 20° in 2 hours. Decomposition with water is then effected, insoluble material is filtered off, and the filtrate is adjusted to pH 5—6 with 2N hydrochloric acid. The precipitated product is extracted with methylene chloride, dried and concentrated by evaporation, whereupon N-(6-chloro-2-dimethylamino-5-pyrimidinyl)dithiocarbamic acid methyl ester crystallises out on the addition of ether and is filtered off. Mp. 150—151°.

**Example 26**

38 g of 6-chloro-2-dimethylamino-4-(dimethylthiomethyleneimino)pyrimidine and 9.2 ml of ethylenediamine in 400 ml of methanol are stirred for 14 hours at 60°. The precipitated 2-(6-chloro-2-dimethylamino-4-pyrimidinyl)amino]-2-imidazoline is isolated by filtration and melts at 278—279°.

The starting material is prepared as follows: 19.8 g of sodium hydride (50% in oil) are added in portions to a solution of 70 g of 4-amino-6-chloro-2-dimethylamino-pyrimidine in 750 ml of dimethylformamide under a nitrogen atmosphere, whilst being cooled with ice and common salt, in such a manner that the temperature does not excess 10°. The mixture is cooled for a further hour in an ice bath until the vigorous evolution of hydrogen ceases. Then 12.3 ml of carbon disulphide are added dropwise whilst cooling at 0—10° and this temperature is maintained for one hour. A further 9.9 g of sodium hydride are added in portions at 0—10°. The reaction mixture is stirred for 30 minutes in an ice bath, after which 6.1 ml of carbon disulphide are added dropwise at 0—10°. The mixture is stirred for a further one hour whilst cooling with ice, then, as described above, is again treated with 9.9 g of sodium hydride and 6.1 ml of carbon disulphide. After addition of the carbon disulphide, the mixture is stirred for a further one hour in the ice bath. Whilst cooling with ice and common salt, 63.4 ml of methyl iodide are then added dropwise within about 30 minutes such that the temperature does not rise above 15°. The cooling bath is then taken away and the mixture stirred for a further 2 hours. 200 ml of water are then slowly added dropwise, whilst cooling with ice, and the reaction mixture is poured onto 2000 ml of water. The precipitated crude product is suction-filtered, thoroughly washed with water and then extracted three times by boiling with 1000 ml of cyclohexane each time. The combined cyclohexane extracts are dried over sodium sulphate, filtered, and concentrated to a volume of approximately 150 ml. On cooling in an ice bath, colourless 6-chloro-2-dimethylamino-4-(dimethylthiomethyleneimino)pyrimidine which melts at 85—87° crystallises out.

In the same manner, 2-[(2,6-dichloro-4-pyrimidinyl)-amino]-2-imidazoline (mp. 215—217°) is obtained from 4-amino-2,6-dichloropyrimidine. 2,6-Dichloro-4-(dimethylthiomethyleneimino)-pyrimidine occurring as intermediate thereby melts at 99—100°.

**Example 27**

4.7 g of 2-[(2,6-dichloro-4-pyrimidinyl)amino-2-imidazoline and 7.8 ml of alcoholic dimethylamine solution (33%) are refluxed for 90 minutes in 30 ml of ethanol. The 2-[(6-chloro-2-dimethylamino-4-pyrimidinyl)amino]-2-imidazoline which has precipitated is suction-filtered whilst still hot and washed with water and ethanol. The product is identical with that of Example 11.

The starting material is prepared according to Example 26.

**Example 28**

One drop of carbon disulphide is added to a mixture of 1 g of 6-chloro-2-dimethylamino-4-

cyanoaminopyrimidine and 0.5 ml of ethylenediamine and the mixture is heated for 1 hour at 100°. The reaction mixture is then concentrated on a rotary evaporator and the residue is suspended in 50 ml of hot ethanol. The insoluble 2-[(6-chloro-2-dimethylamino-4-pyrimidinyl)amino]-2-imidazoline is suction-filtered whilst hot and melts at 264—268°. After recrystallisation from dimethylsulfoxide-methanol the melting point rises to 278—279°.

The starting material is prepared as follows:

1.75 g of sodium hydride (50% in oil) are added in portions to a solution of 6.3 g of 4-amino-6-chloro-2-dimethylaminopyrimidine in 60 ml of dimethylformamide under a nitrogen atmosphere, whilst cooling with ice and common salt, in such a manner that the temperature does not rise above 10°. The mixture is cooled for a further 30 minutes in the ice bath until the vigorous evolution of hydrogen ceases. A solution of 3 g of cyanogen bromide in 30 ml of dimethylformamide is then slowly added dropwise whilst cooling with ice, wherein the temperature should not exceed 20°. When the addition is complete, the mixture is stirred for a further 30 minutes at 0—10°, and is then neutralised with 2N hydrochloric acid. The reaction mixture is poured onto 100 ml of ice water and extracted several times with ethyl acetate. The combined ethyl acetate extracts are dried with sodium sulphate and concentrated. By recrystallisation of the residue from ethanol, crystalline 6-chloro-2-dimethylamino-4-cyanoaminopyrimidine melting at 229—232° is obtained.

**Example 29**

2.9 g (0.01 mole) of 6-chloro-2-dimethylamino-4-(dimethylthiomethyleneimino)-5-methyl pyrimidine and 0.6 g (0.01 mole) of ethylenediamine are dissolved in 50 ml of absolute methyl alcohol and the mixture is stirred for 16 hours at 60°. The mixture is then cooled to room temperature and the precipitated 2[(6-chloro-2-dimethylamino-5-methyl-4-pyrimidinyl)amino]-2-imidazoline is isolated by filtration. The crystallisate is suspended in methyl alcohol, acidified with 5N methanolic hydrochloric acid and the clear solution is concentrated by evaporation under reduced pressure. After recrystallisation of the residue from methyl alcohol-diethyl ether, with the addition of active carbon, 2-[(6-chloro-2-dimethylamino-5-methyl-4-pyrimidinyl)amino]-2-imidazoline hydrochloride which melts at 300° with decomposition is obtained as the colourless crystallisate.

The starting material is prepared as follows:

At 60° reaction temperature, 36.8 g (0.27 mole) of N,N-dimethylguanidine hydrogen sulphate is added to a fresh sodium methylate solution prepared from 12.4 g (0.54 mole) of sodium and 60 ml of absolute methyl alcohol, and the mixture is refluxed for 20 minutes. Thereafter, at reflux temperature a solution of 34.4 g (0.27 mole) of 2-cyanopropionic acid ethyl ester in 110 ml of absolute methyl alcohol is added dropwise within 30 minutes and the white suspension is boiled for a further one hour. After the mixture has cooled, it is filtered, and the filtrate is adjusted to pH 5—6 with 4.5N methanolic hydrochloric acid. The precipitated crystallisate is filtered off and washed with cold methyl alcohol and diethyl ether. After drying in a high vacuum at 70°C, 4-amino-2-dimethylamino-6-hydroxy-5-methylpyrimidine hydrochloride monohydrate of melting point 285—290° is obtained as the colourless crystallisate.

A mixture of 5.0 (0.0244 mole) of 4-amino-2-dimethyl-amino-6-hydroxy-5-methylpyrimidine hydrochloride, 22.3 ml (0.244 mole) of phosphorus oxychloride and 2.55 ml (0.0183 mole) of triethylamine is refluxed for 9 hours, whilst stirring. The excess phosphorus oxychloride is then distilled off under reduced pressure and the viscous oil remaining is discharged onto ice water. The reaction temperature rises as far as 50°. When the reaction has subsided, the mixture is stirred for a further one hour at 60° and is then cooled to room temperature. The pH is adjusted to 7 with concentrated sodium hydroxide solution and stirring is continued for a further one hour at 55—60°C. The pH has to be adjusted by adding concentrated sodium hydroxide solution several times. The mixture is then cooled and extracted four times with 40 ml of chloroform each time. The combined chloroform extracts are dried with sodium sulphate and concentrated by evaporation under reduced pressure. After recrystallisation of the residue from isopropyl alcohol, with the addition of active carbon, 4-amino-6-chloro-2-dimethylamino-5-methylpyrimidine melting at 170—172° is obtained as yellow crystallisate.

0.33 g (0.0069 mole) of sodium hydride (50% in oil) is added to a solution of 2 g (0.0107 mole) of 4-amino-6-chloro-2-dimethylamino-5-methylpyrimidine in 20 ml of absolute dimethylformamide under a nitrogen atmosphere and whilst cooling with ice and common salt, and the mixture is stirred for one hour at 0—5°. 0.2 ml (0.0033 mole) of carbon disulphide is then added whilst cooling at 0—10°C and this temperature is maintained for one hour. A further 0.33 g of sodium hydride is added at 0—5° and stirring is continued for 30 minutes at 0°, whereupon a further 0.2 ml of carbon disulphide is added and the mixture is stirred for one hour whilst cooling with ice. Then, as described above, the mixture is again treated with 0.34 g of sodium hydride and 0.25 ml of carbon disulphide. After the addition of the carbon disulphide, stirring is continued for a further one hour in the ice bath. Whilst cooling with ice and common salt, 1.65 ml (0.0267 mole) of methyl iodide are then added dropwise over the course of approximately 15 minutes such that the temperature does not rise above 10°. The cooling bath is then taken away and the stirring continued for a further 2 hours.

The reaction mixture is then poured onto 50 ml of ice water and extracted three times with 30 ml of ethyl acetate each time. The combined ethyl acetate extracts are dried with sodium sulphate and

concentrated by evaporation under reduced pressure. By extracting the residue by boiling with petroleum ether, mineral oil is removed. To remove moisture and traces of dimethylformamide still adhering, the mixture is treated with toluene, and 6-chloro-2-dimethylamino-4-(dimethylthiomethyleneimino)-5-methylpyrimidine, which is used directly in the form of crude product as starting material, is obtained as the oily residue.

Recrystallisation may optionally be carried out from cyclohexane, a colourless crystallisate which melts at 115—117° being obtained.

The following compounds are also prepared in the same manner:

2-[(2-Methylamino-4-pyrimidinyl)amino]-2-imidazoline; its hydrochloride melts at 275—280°;

2-[(6-Chloro-2-propylamino-4-pyrimidinyl)amino]-2-imidazoline hydrochloride, mp. 230—234°;

2-[(6-Chloro-2-(N-methyl-N-propylamino-4-pyrimidinyl)amino]-2-imidazoline hydrochloride, mp. 187—189°;

2-[(2-Propylamino-4-pyrimidinyl)amino]-2-imidazoline, mp. 230—233°.

The 4-amino-6-chloro-2-propylaminopyrimidine used as starting material can be prepared in the following manner:

A mixture of 12.3 g of 4-amino-2,6-dichloropyrimidine and 16.4 ml of n-propylamine in 700 ml of methyl alcohol is heated to reflux whilst stirring and then the solution, which soon becomes clear, is boiled for a further 16 hours. It is then concentrated by evaporation to dryness under reduced pressure. The residue is rendered alkaline with 2N sodium carbonate solution and extracted several times with chloroform. The combined chloroform extracts are dried with sodium sulphate and concentrated by evaporation. After crystallisation of the residue from petroleum ether, the solution is filtered off and 4-amino-6-chloro-2-propylaminopyrimidine melting at 85—90° is obtained.

The 4-amino-6-chloro-2-(N-methyl-N-propylamino)-pyrimidine used as starting material can be prepared in the same manner as 4-amino-6-chloro-2-propylaminopyrimidine described above, by using N-methyl-N-propylamine instead of n-propylamine for the reaction. 4-amino-6-chloro-2-(N-methyl-N-propylamino)pyrimidine obtained in this manner is used in the form of crude product for the following stage.

The 4-amino-2-propylaminopyrimidine used as starting material can be prepared according to the following process:

With the addition of 0.7 g of a 10% palladium-carbon catalyst, a mixture of 3.7 g of 4-amino-6-chloro-2-propylaminopyrimidine, 140 ml of glacial acetic acid and 30 ml of 2N hydrochloric acid is hydrogenated at room temperature and a pressure of 4 bar until 1 mole equivalent of hydrogen has been absorbed. The mixture is then filtered to remove the catalyst and the filtrate concentrated by evaporation under reduced pressure. The residue is rendered alkaline with 2N sodium carbonate solution, with the addition of ice, and extracted several times with chloroform. The combined chloroform extracts are dried with sodium sulphate, and concentrated by evaporation under reduced pressure. The 4-amino-2-propylaminopyrimidine remaining is used without further purification for the following stage.

**Example 30**

The following compounds may also be prepared analogously to the methods described in the preceding examples:

2-[(2,6-diethoxy-4-pyrimidinyl)amino]-2-imidazoline, mp. 193—195°;

2-[(2-dimethylamino-6-methoxy-4-pyrimidinyl)amino]-2-imidazoline, mp. 90—92°;

2-[(2-isopropoxy-6-methoxy-4-pyrimidinyl)amino]-2-imidazoline mp. 209—210°;

2-[(2-butoxy-6-methoxy-4-pyrimidinyl)amino]-2-imidazoline mp. 184—185°;

2-[(6-chloro-2-isopropoxy-4-pyrimidinyl)amino]-2-imidazoline, mp. 210—211°;

2-[(2,6-bis-dimethylamino-4-pyrimidinyl)amino]-2-imidazoline, mp. 310—312° and

2-[(2-isopropoxy-4-pyrimidinyl)amino]-2-imidazoline, mp. 261—263°.

The starting materials are prepared as follows:

11.5 g (0.5 mole) of sodium are dissolved in 400 ml of absolute alcohol, heated whilst stirring to boiling and, in approximately 20 minutes, 32.8 g (0.2 mole) of 4-amino-2,6-dichloropyrimidine are added in portions. The mixture is then boiled for a further 8 hours, filtered, and the filtrate is evaporated under reduced pressure. The residue is triturated with water, filtered and recrystallised from alcohol. 4-amino-2,6-diethoxypyrimidine melting at 106—108° is obtained.

32.8 g (0.2 mole) of 4-amino-2,6-dichloropyrimidine, 400 ml of isopropanol and a solution of 4.6 g (0.2 mole) of sodium in 100 ml of isopropanol are refluxed for 15 hours. The mixture is concentrated under reduced pressure, the residue is triturated with water and by filtering a crude product is obtained which melts at 108—112°. After recrystallisation from isopropanol, 4-amino-6-chloro-2-isopropoxypyrimidine melting at 125—127° is obtained.

18.8 g (0.1 mole) of the last-named compound are boiled with a solution of 2.3 g (0.1 mole) of sodium in 100 ml of methanol. The mixture is filtered and the filtrate concentrated by evaporation under reduced pressure. The residue is triturated with water, filtered, and recrystallised from methanol. 4-amino-2-isopropoxy-6-methoxy-pyrimidine melting at 89—90° is obtained.

Instead of the cleaned compound, the above described crude product that melts at 108—112° may also be used.

4-amino-2-n-butoxy-6-methoxypyrimidine melting at 94—96° is prepared in an analogous manner.

The resulting 4-amino compounds can be converted into the corresponding S-methyl isothiourea compounds in accordance with Example 1. Their reaction with ethylenediamine yields the corresponding imidazoline products.

**Example 31**

In analogy of the preceding Examples, for example according to Examples 11 and 13, the following compounds may also be obtained:

2-[(2-methyl-6-phenylamino-4-pyrimidinyl)amino]-2-imidazoline. Mp. 263—265°. The hydrochloride melts at 311—313°.

2-[(6-(4-methoxyphenyl)amino-2-methyl-4-pyrimidinyl)-amino]-2-imidazoline. Mp. 266—269°. The hydrochloride melts at 281—283°.

2-[(6-(4-chlorophenyl)amino-2-methyl-4-pyrimidinyl)amino]-2-imidazoline. Mp. 282—284°. The hydrochloride melts at 320—322°.

2-[(2-methyl-6-phenoxy-4-pyrimidinyl)amino]-2-imidazoline. The hydrochloride melts at 302—305°.

The new compounds and their new pre-stages used as starting materials are prepared analogously to those of Examples 11 or 13 as follows:

Ad 1): starting from 4-amino-6-chloro-2-methylpyrimidine and aniline, 4-amino-2-methyl-6-phenylaminopyrimidine, mp. 192—194°, is obtained. After reaction with ethoxycarbonyl isothiocyanate this yields the corresponding ethoxycarbonylthiourea (mp. 199—200°), which is hydrolysed with 1N sodium hydroxide solution to give the corresponding thiourea (mp. 227—230°). The reaction of this thiourea with methyl iodide yields the N-(2-methyl-6-phenyl-amino-4-pyrimidinyl)-S-methylisothiourea hydroiodide used as starting material and which melts at about 150°.

Ad 2): starting from 4-amino-6-chloro-2-methylpyrimidine and *p*-anisidine, 4-amino-6-(4-methoxyphenyl)amino-2-methylpyrimidine, mp. 243—245° is obtained. After reaction with ethoxycarbonyl isothiocyanate in acetone and dimethylformamide this yields the corresponding ethoxycarbonylthiourea (mp. 198—200°), which is hydrolysed with 1N sodium hydroxide solution to give the corresponding thiourea, (mp. 221—224°). The reaction of this thiourea with methyliodide in methanol-dimethylformamide yields the N-[6-(4-methoxyphenyl)amino-2-methyl-4-pyrimidinyl]-S-methylisothiourea hydroiodide used as starting material and which melts at 165—167°.

Ad 3): starting from 4-amino-6-chloro-2-methylpyrimidine and *p*-chloroaniline, 4-amino-6-(4-chlorophenyl)amino-2-methylpyrimidine, mp. 180—182° is obtained. After reaction with ethoxycarbonyl isothiocyanate in acetone and dimethylformamide, this yields the corresponding ethoxycarbonylthiourea (mp. 200—202°), which is hydrolysed with 2N sodium hydroxide solution to give the corresponding thiourea. (Mp. 242—245° with decomposition). The reaction of this thiourea with methyl iodide in acetone yields N-[6-(4-chloro-phenyl)amino-2-methyl-4-pyrimidinyl]-S-methylisothiourea hydroiodide which is used as starting material and melts at 212—215°.

Ad 4): starting from 4-amino-6-chloro-2-methylpyrimidine and sodium phenoxide, 4-amino-2-methyl-6-phenoxypyrimidine (mp. 165—167°) is obtained. After reaction with ethoxycarbonyl isothiocyanate in acetone, this yields the corresponding ethoxycarbonylthiourea (mp. 139—141°), which is hydrolysed with 1N sodium hydroxide solution to give the corresponding thiourea (mp. 221—224°). The reaction of the last-named compound with methyl iodide in methanol-dimethylformamide yields N-(2-methyl-6-phenoxy-4-pyrimidinyl)-S-methylisothiourea hydroiodide used as starting material.

**Example 32**

In analogy to the methods described in the preceding Examples the following compounds may also be prepared: 2-[(4-pyrimidinyl)amino]-2-imidazoline.

2-[(2-butylamino-4-pyrimidinyl)amino]-2-imidazoline.

**Example 33**

Tablets containing 0.1 g of the hydrochloride of 2-[(2,6-dimethyl-4-pyrimidinyl)amino]-2-imidazoline can be manufactured as follows:

*Composition* (for 1000 tablets)

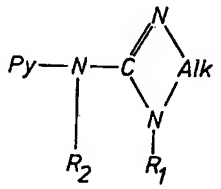
| | |
|---|---|
| 2-[(2,6-dimethyl-4-pyrimidinyl)amino]-2-imidazoline hydrochloride | 100.0 g |
| lactose | 50.0 g |
| wheat starch | 73.0 g |
| colloidal silica | 13.0 g |
| magnesium stearate | 2.0 g |
| talc | 12.0 g |
| water | q.s. |

The 2-[(2,6-dimethyl-4-pyrimidinyl)amino]-2-imidazoline hydrochloride is mixed with a part of the wheat starch, with the lactose and the colloidal silica and the mixture is forced through a sieve. Another part of the wheat starch is made into a paste with 5 times the amount of water on a water bath, and the above power mixture is kneaded with this paste until a slightly plastic mass forms. This is pressed through a sieve of 3 mm mesh width and dried, and the dried granulate is again forced through a sieve. The remaining wheat starch, the talc and the magnesium stearate are added and the resulting mixture is compressed to form 0.25 g tablets.

Tablets or other pharmaceutical preparations which contain a different compound of the invention, for example, one from the preceding Examples, may be manufactured in an analogous manner.

**Claims**

1. A compound of the general formula I



(I)

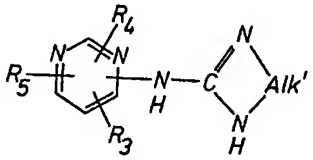
in which Py represents an optionally substituted 4- or 5-pyrimidinyl radical bonded *via* a carbon atom to the nitrogen atom, $R_1$ and $R_2$ independently of one another represent hydrogen, lower alkyl or lower alkenyl, and Alk represents lower alkylene which separates the two nitrogen atoms by 2 to 4 carbon atoms, and their tautomeric compounds.

2. A compound of the general formula I shown in claim 1, in which formula Py represents 4- or 5-pyrimidinyl bonded *via* a carbon atom to the nitrogen atom and optionally substituted by one, two or three identical or different substituents from the group comprising lower alkyl, hydroxy, lower alkoxy, lower alkylthio, halogen, trifluoromethyl, lower alkylsulphonyl, amino; phenyl, phenoxy or phenylamino, each of which can be substituted by lower alkyl, lower alkoxy, hydroxy, amino, lower alkylamino, di-lower alkylamino or halogen; lower aklylamino, di-lower alkylamino, pyrrolidino, piperidino, morpholino, thiomorpholino, lower alkanoylamino, lower alkoxycarbonylamino, ureido, 3-lower alkylureido and 3,3-di-lower alkylureido, and in which $R_1$ and $R_2$ independently of one another represent hydrogen, lower alkyl or lower alkenyl, and Alk represents lower alkylene which separates the two nitrogen atoms by 2 to 4 carbon atoms, radicals denoted by "lower" containing up to 4 carbon atoms, and their tautomeric compounds.

3. A compound of the general formula I shown in claim 1, in which formula Py represents 4- or 5-pyrimidinyl bonded *via* a carbon atom to the nitrogen atom and optionally substituted by one, two or three identical or different substituents from the group comprising lower alkyl, hydroxy, lower alkoxy, halogen, amino; phenyl which can be substituted by lower alkyl, lower alkoxy, hydroxy, amino, lower alkylamino, di-lower alkylamino or halogen; lower alkylamino, di-lower alkylamino, pyrrolidino, piperidino, morpholino, thiomorpholino, lower alkanoylamino, lower alkoxycarbonylamino, ureido, 3-lower alkylureido and 3,3-di-lower alkylureido, and in which $R_1$ and $R_2$ independently of one another represent hydrogen, lower alkyl or lower alkenyl, and Alk represents lower alkylene which separates the two nitrogen atoms by 2 to 4 carbon atoms, radicals denoted by "lower" containing up to 4 carbon atoms.

4. A compound of the general formula I shown in claim 1, in which formula Py represents 4- or 5-pyrimidinyl bonded *via* a carbon atom to the nitrogen atom and optionally substituted by one, two or three identical or different substituents from the group comprising lower alkyl, lower alkoxy, phenyl, amino, lower alkylamino, di-lower alkylamino or morpholino and/or halogen, and in which $R_1$ represents hydrogen or lower alkyl and $R_2$ represents hydrogen or lower alkyl, and Alk represents lower alkylene which separates the two nitrogen atoms by 2 to 3 carbon atoms, radicals denoted by "lower" containing up to 4 carbon atoms, and halogen having an atomic weight of up to 35.

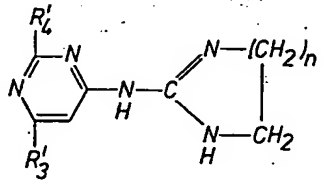
5. A compound of the general formula II



(II)

in which Alk' represents lower alkylene having up to 4 carbon atoms which separates the two nitrogen atoms by 2 to 3 carbon atoms, and each of the radicals $R_3$, $R_4$ and $R_5$ represents hydrogen, lower alkyl having up to 4 carbon atoms, lower alkoxy having up to 4 carbon atoms, halogen, di-lower alkylamino, morpholino or phenyl.

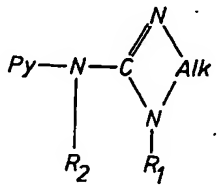
6. A compound of the general formula III



(III)

in which $R_3'$ and $R_4'$ independently of one another represent hydrogen, lower alkyl having up to 4 carbon atoms, lower alkoxy having 4 carbon atoms, halogen or di-lower alkylamino, and n is 1 or 2.

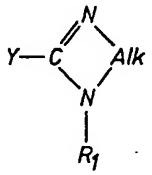
7. 2-[(2,6-Dimethyl-4-pyrimidinyl)amino]-2-imidazoline.
8. 2-[(2,6-Dimethoxy-4-pyrimidinyl)amino]-2-imidazoline.
9. 2-[(4,6-Dimethoxy-2-methyl-5-pyrimidinyl)amino]-2-imidazoline.
10. 2-[(2,6-Dimethyl-4-pyrimidinyl)amino]-1,4,5,6-tetrahydro-pyrimidine.
11. 2-[(6-Chloro-2-methyl-4-pyrimidinyl)amino]-2-imidazoline.
12. 2-[(2-Methyl-4-pyrimidinyl)amino]-2-imidazoline.
13. 2-[(6-Chloro-2-methoxy-4-pyrimidinyl)amino]-2-imidazoline.
14. 2-[(2-Methoxy-4-pyrimidinyl)amino]-2-imidazoline.
15. 2-[(2-Hydroxy-4-pyrimidinyl)amino]-2-imidazoline.
16. 2-[(6-Chloro-2-dimethylamino-4-pyrimidinyl)amino]-2-imidazoline.
17. 2-[(2-Dimethylamino-4-pyrimidinyl)amino]-2-imidazoline.
18. 2-[(6-Chloro-2-diethylamino-4-pyrimidinyl)amino]-2-imidazoline.
19. 2-[(6-Chloro-2-di-n-butylamino-4-pyrimidinyl)amino]-2-imidazoline.
20. 2-[(6-Dimethylamino-2-methyl-4-pyrimidinyl)amino]-2-imidazoline.
21. 2-[(2,6-Dihydroxy-5-pyrimidinyl)amino]-2-imidazoline.
22. 2-[(2,6-Diethyl-5-methyl-4-pyrimidinyl)amino]-2-imidazoline.
23. 2-[(2-Phenyl-4-pyrimidinyl)amino]-2-imidazoline.
24. 2-[(2-Phenyl-4-pyrimidinyl)amino]-1,4,5,6-tetrahydropyrimidine.
25. 2-[(2-Methyl-5-pyrimidinyl)amino]-2-imidazoline.
26. 2-[(5-Pyrimidinyl)amino]-2-imidazoline.
27. 2-[(2-n-Butyl-5-pyrimidinyl)amino]-2-imidazoline.
28. 2-[(2-Phenyl-5-pyrimidinyl)amino]-2-imidazoline.
29. 2-[(6-Chloro-2-(4-morpholino)-4-pyrimidinyl)amino]-2-imidazoline.
30. 2-[(2-Dimethylamino-6-methyl-4-pyrimidinyl)amino]-2-imidazoline.
31. 2-[(2-Diethylamino-5-pyrimidinyl)amino]-2-imidazoline.
32. 2-[(2-Dimethylamino-5-methyl-4-pyrimidinyl)amino]-2-imidazoline.
33. 2-[(2,6-Dichloro-4-pyrimidinyl)amino]-2-imidazoline.
34. 2-[(6-Chloro-2-dimethylamino-5-methyl-4-pyrimidinyl)amino]-2-imidazoline.
35. 2-[(2-Methylamino-4-pyrimidinyl)amino]-2-imidazoline.
36. 2-[(6-Chloro-2-propylamino-4-pyrimidinyl)amino]-2-imidazoline.
37. 2-[(6-Chloro-2-(N-methyl-N-propylamino)-4-pyrimidinyl)-amino]-2-imidazolidine.
38. 2-[(2-Propylamino-4-pyrimidinyl)amino]-2-imidazoline.
39. 2-[(2,6-Diethoxy-4-pyrimidinyl)amino]-2-imidazoline.
40. 2-[(2-Dimethylamino-6-methoxy-4-pyrimidinyl)amino]-2-imidazoline.
41. 2-[(2-Isopropoxy-6-methoxy-4-pyrimidinyl)amino]-2-imidazoline.
42. 2-[(2-Butoxy-6-methoxy-4-pyrimidinyl)amino]-2-imidazoline.
43. 2-[(6-Chloro-2-isopropoxy-4-pyrimidinyl)amino]-2-imidazoline.
44. 2-[(2,6-Bis-dimethylamino-4-pyrimidinyl)amino]-2-imidazoline.
45. 2-[(2-Isopropoxy-4-pyrimidinyl)amino]-2-imidazoline.
46. 2-[(2-Methyl-6-phenylamino-4-pyrimidinyl)amino]-2-imidazoline.
47. 2-[(6-(4-Methoxyphenyl)-amino-2-methyl-4-pyrimidinyl)amino]-2-imidazoline.
48. 2-[(6-(4-Chlorophenyl)-amino-2-methyl-4-pyrimidinyl)amino]-2-imidazoline.
49. 2-[(2-Methyl-6-phenoxy-4-pyrimidinyl)amino]-2-imidazoline.
50. 2-[(4-Pyrimidinyl)amino]-2-imidazoline.
51. 2-[(2-Butylamino-4-pyrimidinyl)amino]-2-imidazoline.
52. An acid addition salt of a compound as claimed in any one of claims 1 to 51.
53. A therapeutically acceptable acid addition salt of a compound as claimed in any one of claims 1 to 51.
54. A pharmaceutical preparation comprising a compound claimed in any one of claims 1 to 51 and 53 in admixture or conjunction with a pharmaceutically suitable carrier.
55. Process for the manufacture of new 2-(pyrimidinylamino)-1,3-diaza-2-cycloalkene compounds of the formula I



(I)

in which Py represents an optionally substituted 4- or 5-pyrimidinyl radical bonded *via* a carbon atom to the nitrogen atom, $R_1$ and $R_2$ independently of one another represent hydrogen, lower alkyl or lower alkenyl, and Alk represents lower alkylene which separates the two nitrogen atoms by 2 to 4 carbon atoms, their tautomeric compounds and acid addition salts, which consists in

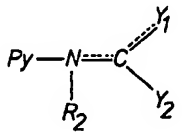
a) reacting a compound of the formula Py—X (IV), or a salt thereof, with a compound of the formula



(V)

or with a salt thereof, wherein one of the radicals X and Y represents an amino group of the formula —$N(R_2)$—H (VI) and the other represents a group that can be split off together with hydrogen under the reaction conditions, or

b) by reacting a compound of the formula



(VII)

in which $Y_1$ represents the imino group, a group that can be split off, the oxo group or thioxo group, and $Y_2$ represents a group that can be split off, or $Y_1$ and $Y_2$ together represent a triple-bonded nitrogen atom, when $R_2$ is hydrogen, or the corresponding tautomeric form, or a salt thereof with an alkylenediamine compound of the formula $H_2N$—Alk—$NHR_1$ (VIII), and if desired, dehalogenating a resulting compound of the formula I, in which the rest Py contains halogen, or replacing the halogen in 2-position by unsubstituted or substituted amino, in a resulting compound in which the rest Py is substituted in the 2-and 6-positions by halogen, and/or, converting any resulting compound into another compound of the invention, and/or, if desired, converting any resulting base into an acid addition salt thereof, or any resulting salt into the corresponding free base or into another acid addition salt, and/or, if desired, resolving a mixture of isomers obtained into the single isomers.

56. The process for the preparation of compounds described in any one of examples 1 to 21.

57. The process for the preparation of compounds described in any one of examples 22 to 32.

58. The compounds prepared according to any one of claims 55 to 57.

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